The Journal of
CLINICAL
ENDOCRINOLOGY

VOLUME 11 DECEMBER, 1951 NUMBER 12
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SEMINAL FRUCTOSE CONCENTRATION AS AN INDEX OF ANDROGENIC ACTIVITY IN MAN*

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THE prosecution of clinical research concerning metabolic and other physiologic properties of male hormone has been seriously handicapped by the lack of a specific sensitive index of either the rate of androgen secretion or the titer of circulating hormone. The measurement of various urinary excretory products which have been suggested for this purpose, has thus far been inadequate. The estimation of urinary 17-ketosteroids and the bio-assay of urinary androgens lack specificity as indicators of testicular androgen output since some of these steroids are derivatives of the adrenals as well as of the testes, and in addition their excretion may be influenced by factors other than glandular secretory activity (1). The excretion of urinary acid phosphatase, derived from the prostate gland, appear too variable from day to day to be useful (2). However, it was thought desirable to pursue the possibility that estimations of other secretory products of the accessory sex glands which require androgen for their development and maintenance, would prove reliable indicators of androgen activity. Accordingly, the present investigation was instituted with the hope that the determination of seminal fructose might serve as a workable assay procedure in man.

It has long been known that seminal plasma contained a yeast-fermentable reducing sugar in concentrations ranging from about 300 to 600 mg.

Received for publication June 5, 1951.
* This work was supported in part by the Douglas Smith Foundation for Medical Research of the University of Chicago.

per cent (3, 4). Huggins and Johnson (3) demonstrated that in man this sugar was secreted by the seminal vesicles, and more recently Mann (5) identified the sugar as fructose rather than glucose, which it had frequently been presumed to be. Subsequently in a series of noteworthy papers Mann and his associates have contributed to an understanding of the biosynthesis of fructose in the accessory glands of various mammalian species and have demonstrated that the fructose is metabolized by spermatozoa (4). It was shown that the formation of fructose was dependent upon the presence of testicular androgen, and very sensitive chemical "hormone indicator tests" were developed in rats and rabbits. Dose-response curves showed a direct relationship between the amount of testosterone administered to castrate rats and the fructose content of seminal vesicles and coagulating glands. Following castration, fructose disappeared from the ejaculate and was restored by the administration of testosterone (6). From these studies, one might expect that the fructose content of human seminal plasma could also be quantitatively related to testicular secretory activity and/or androgen administration.

In these studies we have followed the seminal fructose concentration over a period of months in 4 eunuchoid patients whose androgen intake was carefully controlled and in 1 eunuchoid whose testes were stimulated by the administration of chorionic gonadotropin. In all 5 patients it was possible to demonstrate an influence of androgen on the concentration of seminal fructose. The fructose concentration was also determined in a series of normal semen specimens and compared with the concentrations noted in the ejaculates of men with defective spermatogenesis.

METHODS

All of the semen specimens were secured by masturbation after a period of at least two to four days of abstinence. The ejaculates were collected in clean 40-ml. beakers. As soon after liquefaction as possible, and never exceeding one hour after ejaculation, 0.1 ml. of the ejaculate was quantitatively transferred to 4 ml. of acid cadmium sulfate (13 Gm. of $3CdSO_4 \cdot 8H_2O$ per liter), after which 2 ml. of 0.275 N sodium hydroxide was added, thereby preventing fructolysis. The fructose concentration was subsequently estimated by means of the microglucose procedure of Miller and Van Slyke (7). All values are given in terms of the reduction equivalent of glucose. Although fructose was not specifically determined, on the basis of the previously cited work of Mann *et al.*, it was thought proper to term the reducing sugar estimated by this procedure, fructose. The eunuchoid subjects with the exception of C.A. (Fig. 5) received a daily dosage of methyltestosterone[1] as indicated in the figures. C.A. was given 500 I.U. of

[1] Methyltestosterone (Oreton-M) was generously supplied by Dr. Edward Henderson of the Schering Corporation.

chorionic gonadotropin (APL)[2] intramuscularly three times a week. Spermatozoa counts were performed in the usual fashion, using blood counting chambers and pipettes. Urinary 17-ketosteroids were determined by a modified Holtorff-Koch procedure (8) without employing the correction formula for nonketonic chromogens.

PROTOCOLS

S.S. was a 27-year-old eunuchoid. At the age of 17, sexual development had not occurred, and he was advised that his testes had not descended. Substitution therapy with testosterone propionate was started at this time and continued until shortly before the study reported here. Under the influence of the administered androgen the phallus grew, his voice deepened and beard growth began. He was married and had normal sexual relations. Sexual activity had declined sharply with the cessation of androgen replacement. On physical examination he was moderately obese. The phallus was slightly undersized. The prostate was definitely palpable, small and firm. The scrotum was small and contained small amounts of tissue, but the testes were not identified with certainty. The sella turcica appeared normal on x-ray examination. Urinary 17-ketosteroid excretion was 16 mg. per twenty-four hours.

J.W. was a 21-year-old eunuchoid. Growth and development were normal until the time of puberty, when the absence of sexual maturation was noted. For approximately three years prior to the studies reported here, he had received intermittent weekly and biweekly courses of 25 mg. of testosterone propionate. As a result of this therapy deepening of the voice, slight growth of the phallus and the development of small amounts of pubic and axillary hair were induced. He was 6 ft. 1½ in. tall with disproportionately long limbs. Facial and body hair were fine; axillary hair was sparse, and pubic hair had the feminine conformation. The phallus was prepubertal and the testes pea-sized. A small prostate gland was felt, which was about 3 cm. in diameter. X-ray examination of the skull showed nothing abnormal. Urinary 17-ketosteroid excretion was 8.0 mg. per twenty-four hours. Biopsy of the testis showed small tubules with thin basement membranes. The tubular cells were chiefly spermatogonia and sustentacular cells. Very few Leydig cells were present.

J.K. was 34 years old. His physical and sexual development were apparently normal until the age of 14, when he acquired an acute febrile illness associated with large swollen tender testes. Following this illness, no further development of secondary sex characters was noted. Androgen substitution therapy was begun at the age of 26, followed by restitution of normal sex characteristics and function. Physical examination at the time of these studies showed a normal man, except for the fact that the testes were rather small, being the size of almond kernels. The phallus and prostate were well within the normal limits of size. Beard growth was somewhat less than average.

L.S. was a 28-year-old married eunuchoid whose primary reason for seeking medical assistance was pain in both hips with gradually increasing disability. He had experienced no spontaneous sexual development. At the age of 17, he received two relatively short courses of androgen therapy (of three and six months' duration, respectively) with resultant pubic hair growth and slight enlargment of the phallus. Again at the age of 24, he received two injections a month for a period of a year. He was tall (6 ft. 3¼ in.) and exceedingly thin, weighing only 124 pounds. There was no beard. His skin was youth-

[2] We are grateful to Ayerst McKenna and Harrison for APL (Dr. E. C. Reifenstein, Jr.).

ful. His facial appearance was that of a 15-year-old and his voice was high pitched. The phallus was about the size of a 10-year old boy's. The prostate gland was not palpable. Pubic hair had assumed a feminine pattern. Urinary 17-ketosteroid excretion was 14.5 mg. per twenty-four hours. X-ray examination showed that the sella turcica was normal, the greater trochanters of the femurs had not fused, and that there were changes indicative of moderately advanced aseptic necrosis of both femoral heads.

C.A. was 30 years old. There had been little or no spontaneous sexual development. Late in his teens a sparse growth of pubic hair occurred. At the age of 27 he received a number of injections of testosterone propionate. These resulted in some growth of the phallus, enhanced pubic and axillary hair growth, and deepening of the voice. Sexual desire was increased, and orgasm with ejaculation was possible. No treatment was received for three years prior to the time these studies were begun. He was tall, thin, and immature in appearance, with disproportionately long arms and legs. Facial hair was scant and fine. Pubic hair had the characteristic feminine distribution. The penis was slightly smaller than normal. The prostate gland was not palpable. The testes each measured approximately 1.5 by 2.5 cm. and were quite firm. A roentgenogram showed the skull to be normal, except that the sella turcica was probably small, measuring 8×7 mm. Urinary 17-ketosteroid excretion was 5.1 mg. per twenty-four hours. Biopsy of the testes showed that the seminiferous tubules were small, had thickened basement membranes and were composed entirely of Sertoli cells and spermatogonia. No cells which could be identified with certainty as interstitial cells were seen.

RESULTS

The eunuchoid S.S. (Fig. 1) had been without androgen therapy for sixty days at the time his first semen specimen was analyzed. The fructose concentrations of this ejaculate and of a second one obtained ten days later were exceptionally low (58 and 65 mg. per 100 ml., respectively). When given 10 mg. of methyltestosterone per day (orally), the fructose concentration rose to a level of from 125 to 185 mg. per 100 ml., remaining between these limits for a period of four months. With an increase to 30 mg. of methyltestosterone per day, an additional elevation in the fructose concentration to almost 300 mg. per 100 ml. was secured. A daily dose of 50 mg. of the androgen appeared to induce a further rise in the fructose concentration to a maximum of 516 mg. per 100 ml. After 110 days on lower dosages, the androgen administration was sustained at 50 mg. a day for 220 days, and the fructose concentration of semen specimens obtained during this period varied from 330 to 500 mg. per 100 ml. When the dosage was lowered to 10 mg. daily, the fructose concentration declined, but the lowest point reached during a four-month period was 267 mg. per 100 ml. The average concentration of the ejaculates secured at this level was about 100 mg. per 100 ml. greater than had previously resulted from 10 mg. One month later (not indicated on figure), while taking 5 mg. of testosterone propionate per day by buccal absorption, the fructose concentration of the semen was only 116 mg. per 100 ml., thus showing that much lower seminal fructose concentrations could again be obtained if the quan-

tity of androgen were lowered sufficiently for a long enough period. The patient's subjective evaluation of the androgenic effect at this time was that it was distinctly less than that of 10 mg. per day of methyltestosterone. The volumes of the ejaculates could not be correlated with the dosage of androgen except that, without treatment, the volumes were 0.8 and 1.0 ml., whereas during treatment they ranged from 1.5 to 4.0 ml.

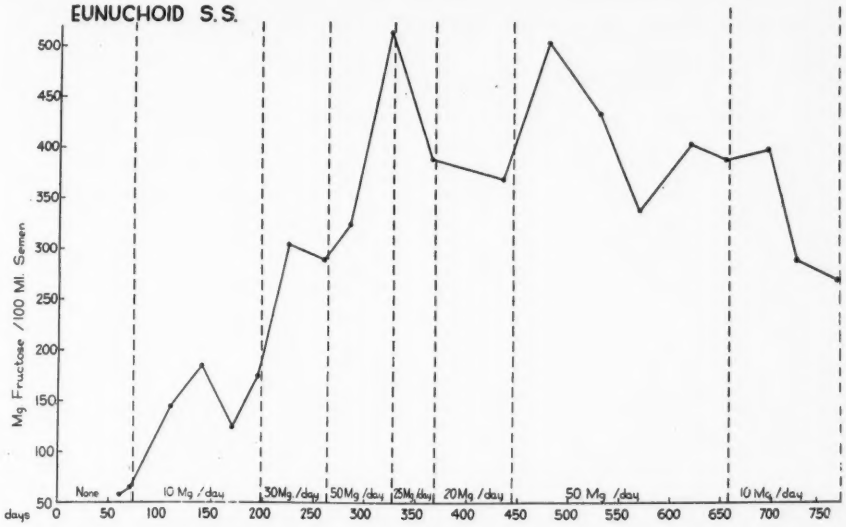

FIG. 1. Semen fructose concentrations at various daily dosage levels of methyltestosterone in the eunuchoid S.S.

The possibility that the lingering effect of the 50-mg. daily dosage influenced all of the values during the second 10-mg. sequence and the concentration in the specimens obtained on days 320 and 430 while the subject was receiving 25 and 20 mg. per day, must be seriously considered. The tendency for the androgenic effect to persist for some days after the cessation of treatment is illustrated in J. W. (Fig. 2). If the values which may have been influenced in the foregoing manner are excluded, the average seminal fructose concentration can be said to rise progressively from the low values before treatment, as doses of 10, 30 and subsequently 50 mg. per day of methyltestosterone were given. The fructose concentration at 50 mg. per day averaged slightly, but significantly, higher than that at 30 mg.[3]

[3] One-tail *t*-test and Wilcoxen test both indicated a moderate significance (0.05 level or better) in the increase in the fructose concentration at a 50-mg. dosage over that obtained on 30 mg. daily.

The first specimen in J.W. (Fig. 2) was secured two weeks after the last of a series of injections of 25 mg. of testosterone propionate given on alternate days. It contained 320 mg. per 100 ml. of fructose. Ejaculates obtained five and fifteen days later showed fructose concentrations of only 122 and 130 mg. per 100 ml., respectively. On 10 mg. per day of methyltestosterone the concentration rose to 265, three additional values at this dosage varying from 230 to 540 mg. per 100 ml. When the androgen was increased to 25 mg. daily, the fructose concentration was sustained at a

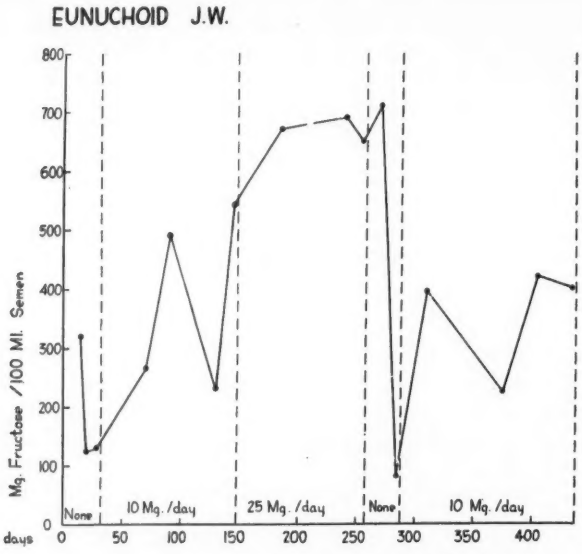

FIG. 2. Semen fructose concentrations at various daily dosage levels of methyltestosterone in the eunuchoid J.W.

level slightly higher than 650 mg. per 100 ml.[4] Two weeks after the medication was discontinued, the fructose concentration was still 710 mg. per 100 ml., but soon afterwards it dropped precipitously to 80 mg. per 100 ml. The return to a 10-mg. dosage of methyltestosterone resulted in approximately the same range of fructose concentration as obtained during the first period on this dosage. Except that the semen volumes were distinctly less without androgen, no relationship to treatment was noted.

While he was maintained on 20 mg. per day of methyltestosterone the seminal fructose concentration in J.K. (Fig. 3) ranged from 360 to 537

[4] One-tail *t*-test and Wilcoxen test both indicated a moderate significance (0.05 level or better) in the elevation in the seminal fructose at a 25-mg. dosage over the values obtained on 10 mg. of methyltestosterone daily.

mg. per 100 ml. Nine days after cessation of treatment the fructose had dropped to 88 mg. per 100 ml. Ten days later, an ejaculate could not be produced and 10 mg. per day of methyltestosterone was again given for a ten-day period. Ten days after this medication was discontinued another semen specimen contained only 84 mg. per 100 ml. of fructose. Subsequently 10 mg. daily of methyltestosterone induced a rise in the

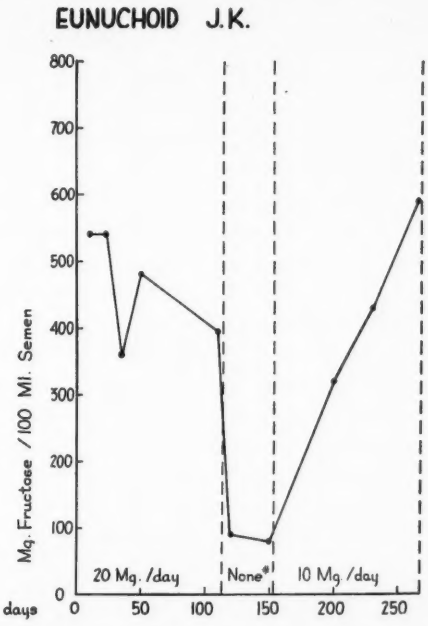

FIG. 3. Semen fructose concentrations at various daily dosage levels of methyltestosterone in the eunuchoid J.K.

* A dose of 10 mg. per day of methyltestosterone was given for ten days beginning ten days after the first ejaculate obtained without treatment.

semen fructose of the same magnitude as that which was attained with 20 mg. Again the volume of ejaculates could not be correlated with the dosage of androgen administered; however, the volumes without treatment were 0.5 ml., whereas the volumes during treatment ranged from 1.0 to 4.5 ml.

Several other eunuchoid subjects were unable to produce a semen specimen when not receiving androgen substitution therapy. In 2 of these individuals, however, ejaculates secured shortly after the institution of small daily doses of androgen contained relatively low concentrations of fructose, which rose as the amount of methyltestosterone administered was

increased. L.S. (Fig. 4) was such a subject. After seven days of treatment with 10 mg. per day of methyltestosterone, the seminal fructose concentration was 117 mg. per 100 ml.; the highest of three values at this dosage was 170 mg. per 100 ml. With an increase in methyltestosterone to 25 mg. daily, the fructose rose from 288 to 429 mg. per 100 ml.

Before treatment was started, but after sever l fruitless efforts, the eunuchoid C.A. (Fig. 5) was able to produce an ejaculate of about 0.1

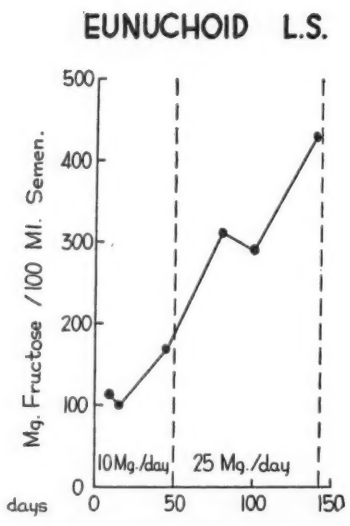

FIG. 4. Semen fructose concentrations at daily dosage levels of 10 and 25 mg. of methyltestosterone in the eunuchoid L.S.

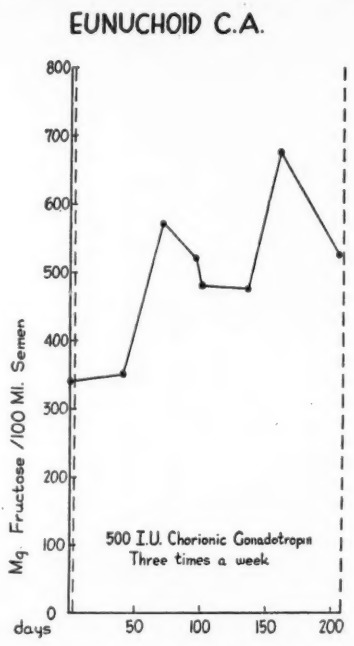

FIG. 5. The effect of chorionic gonadotropin on the semen fructose concentration in the eunuchoid C.A.

ml., which surprisingly contained fructose in a concentration of approximately 340 mg. per 100 ml. After a little over a month of treatment with chorionic gonadotropin an ejaculate was easily obtained (volume 0.7 ml.) but the fructose concentration was not significantly altered. Subsequently, however, as clinical evidence of enhanced testicular androgen secretion became pronounced, the fructose concentration rose and was maintained (6 specimens) at a level of from 475 to 675 mg. per 100 ml. Unfortunately the patient unexpectedly left our care, preventing a post-treatment follow-up period.

Thus, without treatment, the seminal fructose concentrations in 4 of 5 hypogonadal men were either distinctly low, or an ejaculate was unobtainable. If one excludes the initial ejaculates following the cessation of methyltestosterone in J.W. (Fig. 3, days 14 and 275), the seminal fructose concentrations in 3 of these eunuchoid men was always less than 135 mg. per 100 ml., and usually less than 100 mg. when no androgen was being administered. The single exception was noted in C.A. (Fig. 5) whose only pre-treatment value was 340 mg. per 100 ml. In patients S.S., J.W., and L.S. (Figs. 1, 2, and 4), shifts in the dosage of methyltestosterone were reflected by significant differences in the average fructose concentration of several semen specimens.

The determination of seminal fructose in a series of men with no obvious testicular defect and with normal semen specimens, resulted in values (Table 1) which are in substantial agreement with those of other investigators (3). In 24 specimens obtained from 21 men, the fructose concentration ranged from 228 mg. per 100 ml. to 807 mg. per 100 ml., with an interquartile range of 413 to 520. In 12 patients with impaired spermatogenesis but no signs of a testicular secretory deficiency, no tendency toward deviation from the normal was noted. In 14 specimens obtained from 8 men with oligospermia, the range of fructose concentration was from 327 to 784 mg. per 100 ml. (interquartile range, 368-632). In 8 specimens from 5 azoospermic patients, the range was 267 to 664 mg. per 100 ml. with an interquartile range of 464 to 482 mg. per 100 ml. In a majority of the men from whom several ejaculates were obtained on different days, fructose concentrations were in remarkable agreement. Differences of substantially less than 100 mg. were not uncommon and in a few subjects the concentrations of fructose in 2 such specimens were almost identical. It thus appears that when ejaculates are obtained under controlled conditions, in many normal men, in men with impaired spermatogenesis, and in eunuchoids, the fructose concentrations may vary so little that a range characteristic of the individual in a steady state may be established.

DISCUSSION

The utilization of semen fructose concentration as a physiologic index of androgen activity in man is primarily dependent upon a positive correlation between the level of circulating androgen and the concentration of fructose in seminal vesicular secretions. From the studies of Mann and Parsons (6) in rats, such a correlation would be anticipated in man. Since, however, seminal plasma is a mixture of the secretions of the prostate, epididymis and bulbourethral glands as well as of the seminal vesicles, the ultimate concentration of any constituent derived exclusively or almost exclusively from one source would obviously depend upon the relative con-

TABLE 1. FRUCTOSE CONCENTRATIONS IN SEMEN SPECIMENS FROM NORMAL MEN AND FROM PATIENTS WITH OLIGOSPERMIA AND AZOOSPERMIA. VALUES IN BRACKETS INDICATE SUCCESSIVE EJACULATES IN THE SAME SUBJECT

Normal subjects		Oligospermia		Azoospermia
Spermatozoa /cu.ml.	Fructose, mg./100 ml.	Spermatozoa /cu.ml.	Fructose, mg./100 ml.	Fructose, mg./100 ml.
{ 78,000,000	520			
{ 82,000,000	530	Occasional	327	647
110,000,000	459	{ 7,000,000	335	267
		{ Occasional	252	
320,000,000	423	{ 4,600,000	432	{ 464
		{ Few	390	{ 467
190,000,000	226			664
128,000,000	484	{ 110,000	632	{ 482
		{ 900,000	668	{ 476
71,000,000	292	{ Occasional	846	
				282
80,000,000	484	{ 8,000,000	471	
		{ 16,000,000	481	
152,000,000	632			
		13,000,000	658	
61,000,000	400			
		{ 450,000	411	
100,000,000	228	{ Occasional	381	
59,000,000	262	Occasional	368	
{ 61,000,000	642			
{ 102,000,000	501			
{ 19,000,000	446			
{ 110,000,000	413			
219,000,000	434			
70,000,000	210			
213,500,000	807			
138,000,000	504			
70,000,000	660			
152,000,000	666			
150,000,000	460			

tribution of that gland. Accordingly the size and storage capacity of each of the glands and the efficiency of the ejaculatory mechanism must be considered as additional factors affecting the fructose concentration of semen. Variations in the contribution of individual accessory glands must account at least in part for the wide range in seminal fructose concentrations observed in different individuals. On the other hand, it is apparent from these studies that when ejaculates are collected under standard conditions, the fructose concentration in a given subject frequently remains within relatively narrow limits, suggesting that the proportional contribution of the seminal vesicles is fairly constant from specimen to specimen. With such constancy, shifts in circulating androgen which result in altered secretory activity of the seminal vesicles might well be reflected in the whole-semen fructose concentration.

The rising seminal fructose concentration which was induced by the administration of androgen to hypogonadal men indicates that this occurs, and that, although it has its limitations, this chemical indicator test probably offers the possibility of developing into the most sensitive specific androgen assay procedure yet available in man. In all instances in which the seminal fructose concentration was 135 mg. per cent, or less, signs of testicular deficiency were pronounced; and in all cases treatment with androgen was followed by highly significant elevations in the seminal fructose. In several of the eunuchoids (Figs. 1, 2 and 4) the semen fructose concentration not only rose with androgen therapy, but the level of fructose in the semen could be correlated with the quantity of androgen administered.

Finding an essentially normal fructose concentration in the semen of a man who was hypogonadal by all clinical criteria (Fig. 5) was somewhat disturbing. It is possible, however, that in this individual amounts of circulating androgen insufficient to induce full sexual maturation but nevertheless great enough to preserve some seminal vesicular function, were present. The fact that C.A.'s testes were successfully stimulated with chorionic gonadotropin suggests that minute quantities of androgen sufficient to support minimal seminal vesicular function could have been secreted prior to therapy. However, even in this exceptional instance, higher fructose concentrations resulted from enhanced androgenic stimulation of the seminal vesicles.

Although the data are not complete on the point, it would appear that the hypogonadal men were not equally sensitive to methyltestosterone. J.K. (Fig. 3) showed no difference in the response to 10 and 20 mg. of methyltestosterone per day, suggesting that the fructose concentrations at a 10-mg. level were maximal. In J. W. the fructose concentration rose as the dosage was increased to 20 mg. daily, but the values at this level

were so close to the maximal noted in man that it is highly unlikely that 50 mg. could have induced a greater rise. L.S. was also responsive up to a dosage of 25 mg. per day, but larger amounts were not given. In S.S (Fig. 1), on the other hand, the seminal fructose concentration rose progressively with each increment in androgen dosage from 10 to 50 mg. per day. Such variations may be ascribed to differences in the absorption and metabolic handling of methyltestosterone as well as to differences in the sensitivity of peripheral tissues.

From the experience reported here, one can be guided toward the development of an androgen-assay procedure in which the androgenicity of a material to be tested can be estimated by comparing its effect upon the seminal fructose concentration of a hypogonadal man with that of a standard substance in the same individual.

The selection of suitable subjects for assay purposes would involve several practical difficulties. The proper individuals must be healthy, hypogonadal males (castrate or eunuchoid); for instance, diabetics would be unsatisfactory since the seminal fructose is elevated in association with hyperglycemia (6, 9). The subject must be willing to follow arbitrary changes prescribed in the therapeutic regimen and to produce specimens of semen in the Clinic at fairly frequent intervals. In addition, repeated ejaculates obtained under such standard conditions should contain much the same fructose concentration. Because, even in the more satisfactory patients, differences of 150 mg. per 100 ml. in the fructose concentration on a fixed androgen intake are not unusual, it would be highly desirable to secure at least three ejaculates at each dosage level.

Such dose-response comparisons should always be carried out on an ascending androgen dosage. On two occasions in J.W. (Fig. 2) moderate to high fructose concentrations persisted for two weeks after the androgen was discontinued. And in S.S. (Fig. 1) the fructose concentration declined very slowly after the dosage of androgen was decreased, suggesting that the influence of higher dosages may be considerably prolonged during a succeeding period of diminished androgen administration. An interval of several weeks without treatment should accordingly be interposed whenever there is a change to a lower dose of androgen.

The minimum time required to reach the characteristic or base-line fructose concentration for each dosage of androgen has not been determined. Certainly such a level was reached in thirty days in each of the eunuchoids who received methyltestosterone and may well have been attained within two weeks, as shown in L.S. (Fig. 4). Once the characteristic fructose concentration for a given quantity of androgen has been established, the level may be maintained as shown for at least three to six months.

It is clear from these studies in hypogonadal men and from the data collected in various series of normal men and patients with impaired spermatogenesis that unless the fructose concentration of an isolated specimen of semen is in the neighborhood of 100 mg. per 100 ml., no information concerning the internal secretory activity of the testes can be secured from this procedure. Although in our experience all patients whose seminal fructose concentration has been 135 mg. per 100 ml. or less have been hypogonadal, the wide spread of concentrations observed in normal men and the normal value in 1 eunuchoid patient prevent our drawing any conclusion concerning the meaning of a single value within the range of from 200 to 800 mg. per 100 ml. However, by following the seminal fructose in serial fashion in an individual in whom the concentration of fructose normally remains relatively constant from specimen to specimen, it is quite possible that alterations in the internal secretory activity of the testes may be reflected by significant shifts in the level of seminal fructose. Thus an elevation in the fructose concentration would indicate an enhanced secretion, and a decline, a drop in the output of testicular androgen. It is apparent, however, from the studies in eunuchoids that only changes in secretory activity which were sustained for some days could be indicated by this procedure.

Although it has been noted elsewhere (10) that azoospermic ejaculates contained a higher reducing-sugar concentration than normal specimens, no evidence can be adduced from these studies to suggest that defects in spermatogenesis are consistently associated with, or attributable to, an androgen excess or deficiency. In neither the series of oligospermics nor azoospermics was the interquartile or gross range of fructose concentrations significantly different from those of normal men.

SUMMARY

1. In man, seminal fructose is derived almost exclusively from the seminal vesicles, which are dependent upon androgen stimulation for their maintenance.

2. The semen fructose concentration may range from 200 to 800 mg. per 100 ml. in men with apparently normal testicular function, whereas fructose concentrations of less than 135 mg. per 100 ml. have been noted only in distinctly hypogonadal men. The administration of androgen to a eunuchoid patient was invariably followed by a highly significant elevation in the seminal fructose.

3. With a fixed dosage of androgen in eunuchoids, and under standardized conditions in other subjects, the fructose concentration of individual ejaculates generally remained within relatively narrow limits.

4. In 3 eunuchoids, levels of seminal fructose concentration character-

istic of each of several dosages of administered androgen were obtained. This dose-response relationship indicates that, given a suitable hypogonadal subject, the estimation of seminal fructose concentrations may well be developed into a highly specific means of evaluating the androgenicity of hormonal substances in man.

5. One eunuchoid patient, untreated for several years, had a seminal fructose concentration in the normal range, suggesting the presence of minimal testicular androgen output.

6. It is possible that, if serial ejaculates are examined, sustained alterations in the testicular hormone output of the normal man might be reflected in shifts in the fructose concentration of semen.

7. No evidence of an androgen deficiency or excess could be adduced from the seminal fructose concentrations of patients with oligospermia or azoospermia.

Acknowledgment

The authors would like to acknowledge the helpful encouragement of Dr. A. T. Kenyon and the statistical advice of Dr. Jimmy Savage.

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β-GLUCURONIDASE STUDIES IN WOMEN. V. THE MENSTRUAL CYCLE:

AND SERUM β-GLUCURONIDASE ACTIVITY IN ESTROGEN-TREATED POSTMENOPAUSAL SUBJECTS*†

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IN THE course of clarifying the significance of β-glucuronidase activity in the vaginal fluid for detecting the presence of cancer of the cervix (1, 2), it was found that endocrine factors had an important influence. For instance, high vaginal fluid β-glucuronidase titers were frequently found in postmenopausal women and in women who had been castrated by surgery or irradiation. It seemed logical therefore to investigate β-glucuronidase activity of the vaginal fluid as a function of the menstrual cycle in healthy young women and to explore the effects of estrogen on β-glucuronidase in various physiologic states.

PLAN OF STUDY

Sixteen healthy young women collected their own vaginal fluid specimens twice a week according to the technique described in a previous paper(1). Resting morning temperatures were recorded daily. β-Glucuronidase activities were determined in the laboratory on the day of collection, as previously described (1), both on vaginal fluid and on blood serum. Many of these individuals were followed through three complete menstrual cycles. The data were graphed and then grouped into two categories, the first being the women with 28-day (±3 days) cycles and the second representing 35-day (±3 days) cycles. All of these women menstruated regularly within the limits of these two groups. Malignancy

Received for publication June 16, 1951.

* This work was supported by grants-in-aid from the National Cancer Institute of the National Institutes of Health, United States Public Health Service, Bethesda, Maryland, the Damon Runyon Memorial Fund for Cancer Research, New York, and by an institutional grant of the American Cancer Society, Inc., New York.

† Presented at the 42nd Annual Meeting of the American Association for Cancer Research, Inc., Cleveland, April 27–29, 1951.

of the genital tract was ruled out by repeated examination of the Papanicolaou smears.

One of the subjects (Case 5) of the control study was a 36-year-old married female who later underwent panhysterectomy with bilateral salpingo-oophorectomy for a leiomyomatous uterus. Subsequently, beginning one month after operation, her vaginal fluid and blood were assayed regularly for almost four months. During the fourth postoperative month she re-

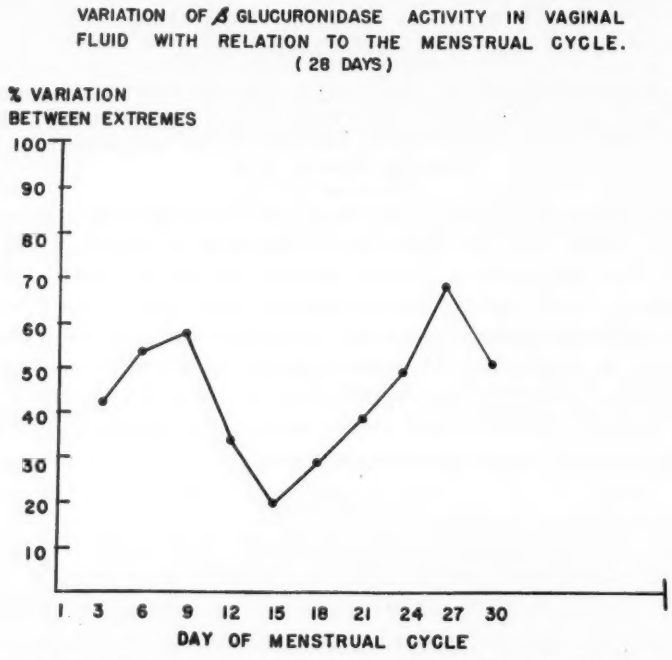

FIG. 1. Variation of β-glucuronidase activity in vaginal fluid with relation to the menstrual cycle (28 days). (Composite of average values; *see* text.)

ceived stilbestrol orally in a dose of 1 mg. three times a day and in addition, after two weeks, progesterone, 10 mg. twice a day for fourteen days. Her data have been graphed in relation to time and physiologic status.

The effect of stilbestrol on vaginal fluid and blood β-glucuronidase in postmenopausal women was investigated in 10 subjects receiving 5 mg. of stilbestrol daily for twenty-one days. Specimens were collected for a week or two after stilbestrol administration. Six other subjects were given daily stilbestrol at dosage levels of 1, 5, and 10 mg. for varying lengths of time, interrupted by periods free of medication.

RESULTS

Normal menstrual cycles and β-glucuronidase activity in vaginal fluid

Figure 1 represents a composite plot of the vaginal fluid β-glucuronidase activity as a function of time in a 28-day menstrual cycle and Figure 2, in a 35-day menstrual cycle. β-Glucuronidase activity has been expressed

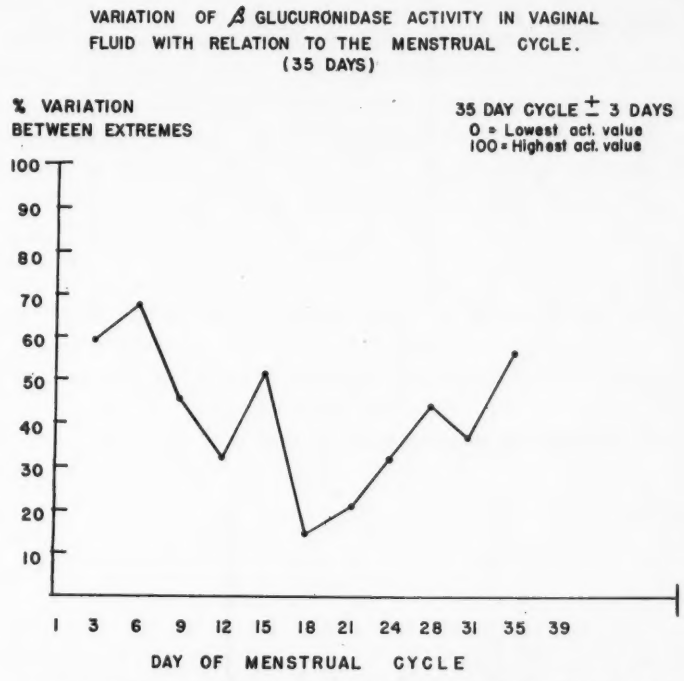

FIG. 2. Variation of β-glucuronidase activity in vaginal fluid with relation to the menstrual cycle (35 days).

as the percentage of the extreme values measured in the course of the study of a given subject. This was necessary in order to construct an intelligible composite figure. The enzyme values ranged from 0 to 300 units per gram, but occasional individual patients exhibited values from 400 to 700 units per gram and sometimes even higher. However, the curves showed consistent contours with a low range of values corresponding to mid-cycle and values higher than this in the week before and after the menses. Figure 3 shows resting body temperatures and vaginal fluid enzyme activity correlated with the events of the menstrual cycle in a typical patient.

There was no consistent correlation of the blood serum β-glucuronidase activity with phases of the menstrual cycle.

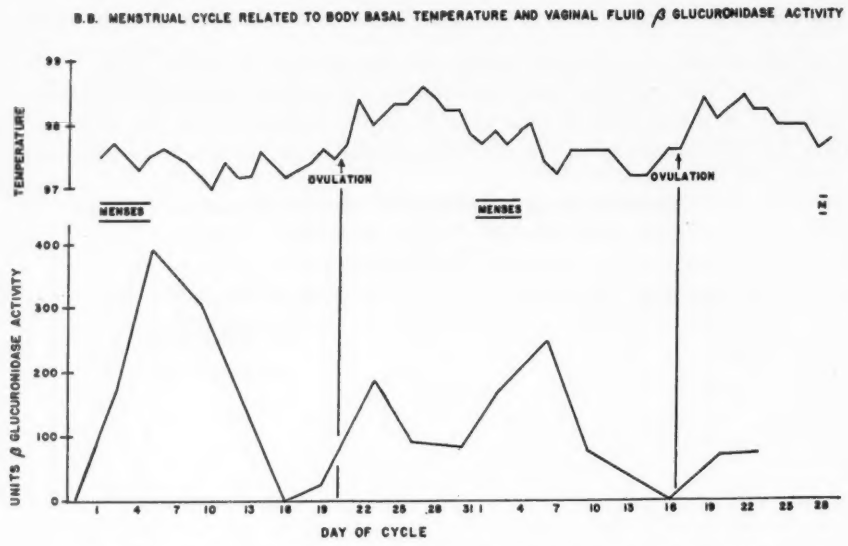

FIG. 3. Menstrual cycle related to body basal temperature and vaginal fluid β-glucuronidase activity.

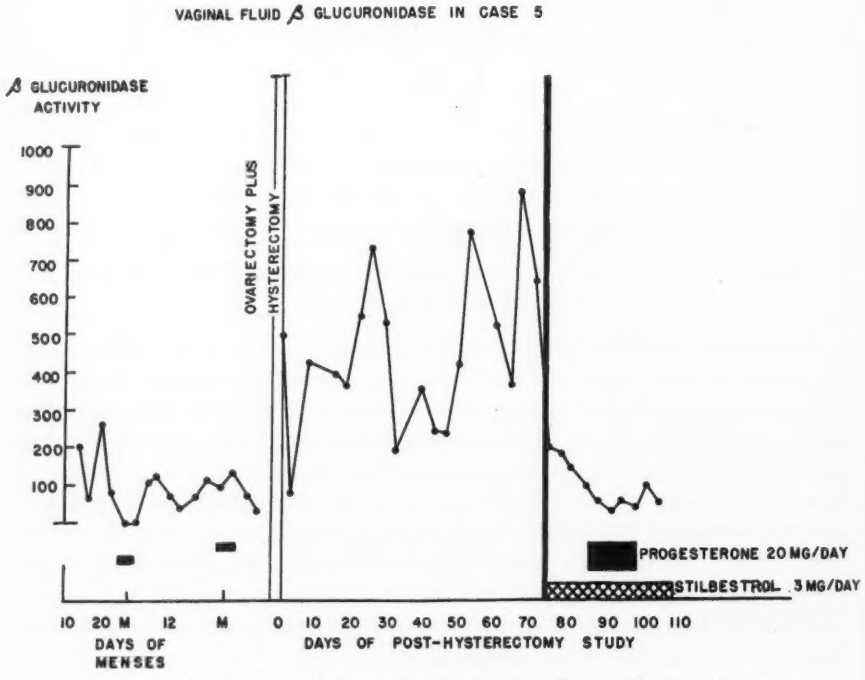

FIG. 4. Vaginal fluid β-glucuronidase in Case 5. The post-hysterectomy study began one month after surgery.

Effect of castration on β-glucuronidase activity in vaginal fluid

Figure 4 illustrates the data in Case 5. The patient underwent surgical castration and panhysterectomy. One month following operation the vaginal fluid β-glucuronidase activity was elevated and fluctuated at higher levels until she was given stilbestrol, whereupon it fell to preoperative levels.

Effect of stilbestrol administration on blood serum β-glucuronidase in postmenopausal women

Following administration of physiologic doses of stilbestrol to postmenopausal patients, blood serum β-glucuronidase showed an unquestionably significant rise in 8 out of 10 patients (Fig. 5). The values in Patients B.S. and R.G. were considered equivocal. As a rule, the response of the

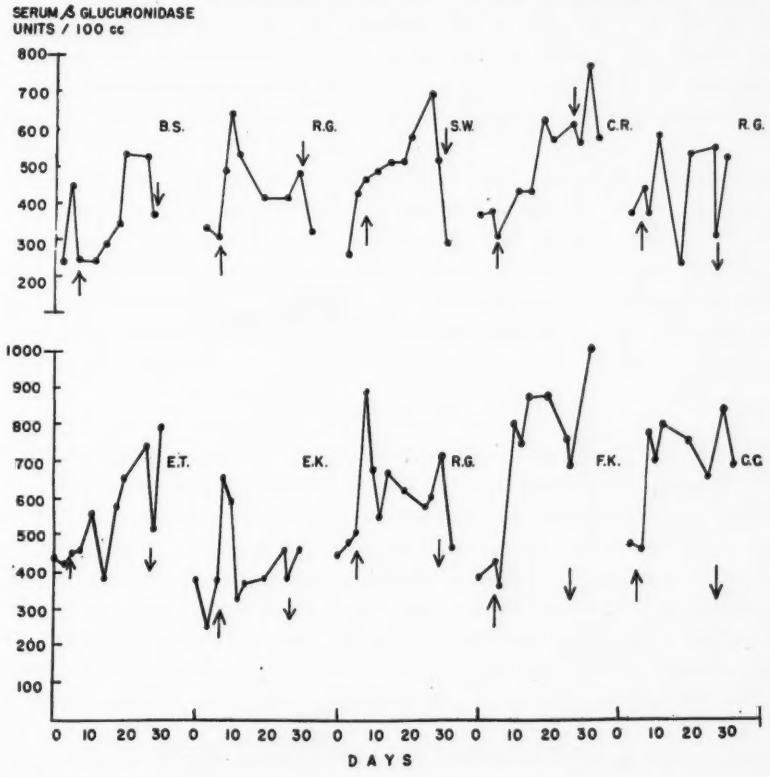

FIG. 5. Effect of stilbestrol (5 mg./day for twenty-one days) on serum β-glucuronidase activity in postmenopausal subjects. The upward arrow indicates the initiation of therapy and the downward arrow, cessation of therapy.

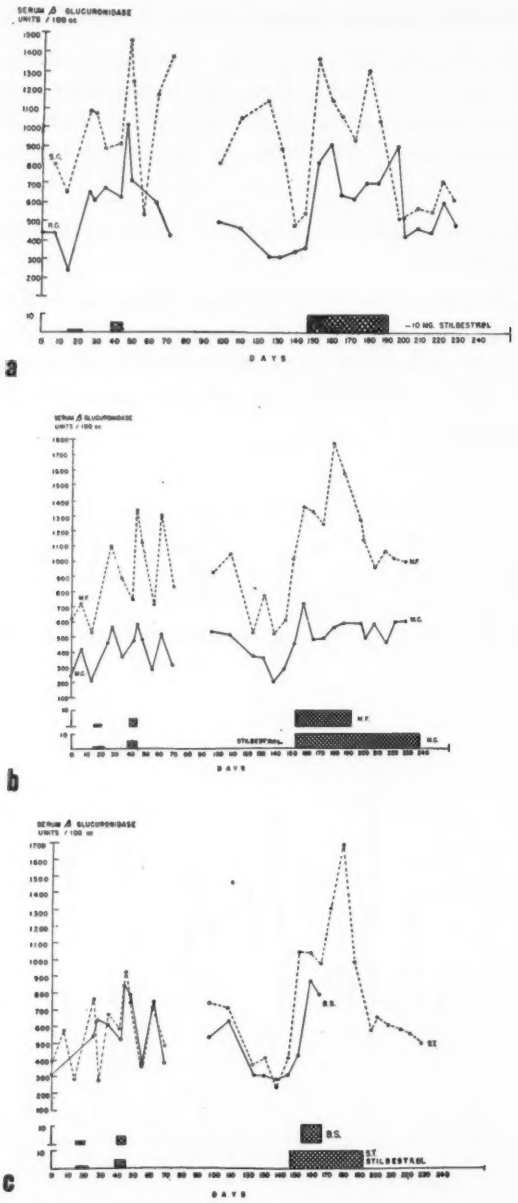

FIG. 6 *a*, *b* and *c*. Effect of stilbestrol (various amounts and durations of dosage) on serum β-glucuronidase in postmenopausal subjects. Stilbestrol dosage (mg.) is plotted for each patient in *b* and *c*, since the dosage was not uniform.

serum β-glucuronidase was rapid and elevated enzyme levels were maintained until stilbestrol was discontinued. Four days later, the enzyme level fell markedly in 3 out of these 8 subjects but not in the others.

In 6 other subjects (Fig. 6 *a*, *b*, *c*) three oral dosage levels were employed in each, 1 mg. and 5 mg. daily for a week, and 10 mg. daily for from twelve to eighty-five days.

At the 1-mg. stilbestrol dosage level, 3 subjects (R.G., S.C. and M.F.) exhibited a clear-cut elevation in serum β-glucuronidase and in all 6 subjects the value after stilbestrol therapy surpassed the highest control value. In the two weeks intervening before the next course of stilbestrol, the serum enzyme remained elevated in patients R.G. and S.C.

Upon administering 5 mg. of stilbestrol daily for a week, a rise of the serum β-glucuronidase occurred by the end of the fourth day in all 6 subjects. The values in all 6 instances exceeded the maximum attained during the administration of 1 mg. of stilbestrol daily. The subjects received no medication for the next 103 to 110 days. In all 6 subjects wide fluctuation in serum β-glucuronidase activity persisted for a period of eighty to ninety-five days, after which more or less stable levels of the serum enzyme were observed.

The next period of stilbestrol administration (10 mg. daily) produced a marked increase in serum β-glucuronidase within four days, which was maintained throughout therapy. Upon discontinuation of stilbestrol the enzyme levels fell and stabilized themselves at activities somewhat higher than the pretreatment values. Patient D.S. died of a coronary occlusion after twelve days of stilbestrol. Patient M.C. was continued on stilbestrol for eighty-five days.

DISCUSSION

β-Glucuronidase activity is correlated with the action of estrogenic hormones. Upon castration of adult female mice, the uterine tissue β-glucuronidase decreases markedly and can be restored to normal levels by physiologic amounts of estrogen (3). Human endometrial tissue possesses high β-glucuronidase activity which undergoes change during the menstrual cycle (5). Human serum β-glucuronidase activity increases progressively with gestation and after parturition falls to pregestational levels in five to ten days (6, 7). Administration of stilbestrol for ten days post partum either prevents or reduces the extent of the decrease in serum β-glucuronidase activity (8).

The activity of β-glucuronidase may be a function also of nonestrogenic factors. For the purpose of the present discussion, however, we need concern ourselves only with the estrogen-enzyme relationship.

β-Glucuronidase activity can be demonstrated in many body fluids and

secretions (9) including the vaginal fluid (10, 1). In connection with the suggested use of β-glucuronidase levels in vaginal fluid as a means of detecting cancer of the cervix uteri, we undertook a systematic study of the physiologic factors which influence vaginal fluid β-glucuronidase activity. It was found that high β-glucuronidase activities were observed more frequently in women after the physiologic menopause and after surgical or radiologic castration (1). The presence of the uterus and cervix were not necessary to explain β-glucuronidase activity of vaginal fluid, since high enzyme levels were found in the blind pouch remaining after panhysterectomy. *Trichomonas vaginalis* infestation (11) and vaginal leucocyte population (12) are factors of minor significance in explaining high vaginal fluid β-glucuronidase values. Premenopausal women with untreated cancer of the cervix uteri have a range of β-glucuronidase activity similar to that observed in postmenopausal women with or without cancer.

It is of obvious interest, therefore, to determine the relationship between vaginal fluid β-glucuronidase activity and the events of the menstrual cycle. The present data indicate a biphasic variation in values with a low region of levels corresponding to the mid-menstrual period. In the 28-day cycle the low point occurs on day 15 and in the 35-day cycle on day 17. Employing the resting body temperature readings as an indication of the time of ovulation, the low region of vaginal fluid β-glucuronidase activity bore a close relation to the rise in body temperature. It should be noted that the composite curves in Figures 1 and 2 have only a qualitative significance, justifying the previous statements but possessing little value as a quantitatively reproducible figure in any given woman.

The question now arises: "Why does the β-glucuronidase activity of vaginal fluid diminish at a time when ovulation presumably occurs?" Several possibilities exist. One is a direct effect of estrogens or of progestational hormones on the elaboration of β-glucuronidase by the epithelial cells of the vaginal mucosa. Another is an effect of estrogen or of progestin on the release of enzyme from tissue cells into extracellular fluid. Both the action of estrogen or progestin may be secondary to pituitary secretion. A third is the possibility that at ovulation the increased secretion of cervical mucus, which may be poor in β-glucuronidase, may serve to dilute the vaginal fluid enzyme. It is conceivable also that an inhibitor, perhaps similar to one in blood (13), appears in the vaginal fluid at mid-cycle. Perhaps the reduction in leucocytes in the vaginal fluid occurring at mid-cycle may explain the low values.

On the basis of our present information, the vaginal tissue would be expected to increase its β-glucuronidase activity during the follicular phase of the menstrual cycle. According to Harris and Cohen (14), progesterone reduces the rodent vaginal tissue β-glucuronidase activity which has been

previously stimulated by estrogen administration. If human vaginal tissue behaved similarly and if the release of enzyme from tissue cells into vaginal fluid is not a factor, the simplest explanation for the low vaginal fluid β-glucuronidase at mid-cycle would be the initiation of progestin's depressing action on β-glucuronidase activity.

Ovarian function and vaginal fluid β-glucuronidase

The subject (Case 5) in whom ovariectomy and panhysterectomy had been performed, was studied to clarify the role of ovarian function in explaining vaginal fluid β-glucuronidase activity. Since the removal of the ovaries results in a rapid increase in vaginal fluid β-glucuronidase activity, it would seem that in premenopausal women the ovaries ordinarily exert an inhibitory effect on the enzyme. The biphasic phenomenon in the menstrual cycle of β-glucuronidase in vaginal fluid as an ovarian function has been discussed in a preceding section of this article. In postmenopausal women, therefore, the frequent occurrence of high vaginal fluid β-glucuronidase may be related to declining ovarian function. The presence of the uterus is considered to be of little significance in explaining vaginal fluid β-glucuronidase since in a previous study (1) noncastrated women, in whom hysterectomy had been performed, exhibited a normal range of vaginal fluid enzyme levels.

Administration of estrogen in Case 5 resulted in a precipitous fall in the vaginal fluid β-glucuronidase to low levels which were maintained throughout the course of estrogen therapy, with or without progesterone treatment. This action of stilbestrol has duplicated the low levels of vaginal fluid β-glucuronidase which existed in this subject at the time her ovaries were functionally intact. The logical conclusion to be drawn from this study is that under physiologic conditions, ovarian estrogen exerts a depressing action on vaginal fluid β-glucuronidase. Just as with the menstrual studies, the exact mechanism of this vaginal phenomenon remains to be elucidated.

Blood serum β-glucuronidase in postmenopausal women

It was of interest in connection with the vaginal fluid studies to investigate the effects of estrogen on the blood serum β-glucuronidase in postmenopausal women. Altogether 14 out of 16 women who were studied showed a significant elevation in the serum enzyme following stilbestrol administration. In some of these subjects, the increase occurred within four days and in others, effects were seen with as little as 1 mg. of stilbestrol per day for seven days. It seems, therefore, that the serum β-glucuronidase is highly sensitive to estrogen administration. Immediately after cessation of estrogen administration some subjects showed a rapid fall, whereas others

showed no change or further increase in serum levels of the enzyme. In 6 patients followed for fifty to one hundred days after a course of stilbestrol (5 mg./day for one week), marked fluctuations in the serum β-glucuronidase were observed. This may suggest that if these enzyme variations reflect an endocrine imbalance induced by stilbestrol, the clinical effects of the estrogen may be of much longer duration than is appreciated. The study of vaginal fluid β-glucuronidase activity in these subjects yielded data which frequently showed a depression of the vaginal fluid β-glucuronidase.

The source of the additional enzyme activity observed in the serum of stilbestrol-treated women is not known. If this activity is due to newly formed enzyme protein, the tissue(s) which produce(s) it must be capable of the rapid generation and release into the circulation of β-glucuronidase. Preliminary experiments (15) indicate that in C_3H mice stilbestrol will increase liver β-glucuronidase content, which would be the only evidence at present available suggesting a site of β-glucuronidase formation or storage.

The elevation in serum β-glucuronidase noted during pregnancy would seem to be explained, from our present data, on the basis of increased estrogen production and metabolism.

Of interest also is the report of Cohen and Huseby (16) who found the serum β-glucuronidase in women with cancer of the breast to respond to estrogen administration.

SUMMARY

The activity of β-glucuronidase in the vaginal fluid has been correlated with the events of the menstrual cycle in normal healthy women. Low values were consistently found at mid-menstrual cycle in women whose periods were of twenty-eight and of thirty-five days' duration. One of these subjects underwent ovariectomy and panhysterectomy, following which the vaginal fluid β-glucuronidase rose to a much higher level. At that time, administration of estrogen resulted in a rapid fall in the β-glucuronidase activity of her vaginal fluid.

The majority of postmenopausal women given a course of stilbestrol therapy exhibited an elevation in blood serum β-glucuronidase. This response was demonstrated with amounts of stilbestrol as low as 1 to 5 mg. per day for seven days. These findings are discussed in relation to the factors which control β-glucuronidase activity in vaginal fluid and in blood.

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THE OCCURRENCE AND SIGNIFICANCE OF LEYDIG CELL PROLIFERATION IN FAMILIAL ADRENAL CORTICAL HYPERPLASIA*†

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INTRODUCTION

FAMILIAL (congenital) adrenal cortical hyperplasia, the most common cause of the adrenogenital syndrome, has been the subject of a progressively increasing number of papers. Clinically, affected males commonly show gastrointestinal disturbances in the neonatal period, and later accelerated growth, exaggerated masculinization, and relative enlargement of the sexual organs (macrogenitosomia). The majority show Addisonian symptoms of varying degrees of severity, and die in Addisonian crisis, the longest reported survival of an affected male being 20 years (1). Affected females usually have an enlarged clitoris at birth, and are commonly mistaken for males with hypospadias; later they also show accelerated growth and increasing masculinization, so that many are raised as boys and a few marry as males. Addisonian symptoms are relatively rare in affected females (2, 3), and many reach middle or advanced age, probably the oldest reported having been 79 years old (4). In recent years, particular attention has been devoted to the Addisonian symptoms (5–11). Because these symptoms tend to be more difficult to regulate with desoxycorticosterone and salt in these patients than in those with other forms of Addison's disease, it has been postulated that the abnormal adrenals make a hormone or hormones which interfere with the action of desoxycorticosterone acetate (DCA) (12). As a result, in an effort to control the symptoms in these subjects more easily, total adrenalectomy has recently been attempted (7), subtotal adrenalectomy having been found repeatedly to be of no benefit (13, 14). Recently, also, cortisone has been shown to decrease 17-ketosteroid production in these patients and the degree of masculinization in affected females (15–17).

These therapeutic advances have stimulated renewed interest in the

Received for publication June 30, 1951.

* This investigation was supported in part by a research grant from the National Cancer Institute of the National Institutes of Health, Public Health Service, and in part by the Children's Cancer Research Foundation.

† Read by title at the meeting of the American Association of Pathologists and Bacteriologists, Cleveland, Ohio, April, 1951.

question of the cause of this disease, but the problem of whether the basic abnormality lies in the pituitary (18) or in the adrenal (15) is as yet unsettled. A number of male patients with this disease have been reported to have nodules of "aberrant adrenal cortical tissue" within the testes (10, 16, 19–22) or to have "bilateral adrenal cell tumors" of the testes (1). Possibly similar lesions have been observed in the ovaries of a smaller number of females (4, 23–26). A few authors (18, 24) have suggested that these nodules are composed of Leydig cells or their ovarian homologue, the hilar cells. If this latter suggestion could be verified, the theory that the primary disorder in the disease lies in the pituitary would receive strong support, since the conclusion that the adrenal cortices and the Leydig cells are both stimulated by the pituitary is more tenable than the alternative explanation that both are primarily abnormal. The recent opportunity to study 3 cases of familial adrenal cortical hyperplasia in male infants has provided an opportunity to study the nature of these testicular nodules, as well as the findings in the pituitaries, in an attempt to analyze the nature of this disease.

REPORT OF CASES

Case 1.—A white male infant was born by traumatic forceps delivery after an 8-hour labor induced ten days prior to term because of pre-eclampsia. Birth weight was 9 pounds, 3 ounces, and the infant was discharged from the hospital on the ninth day of life. On the eleventh day, vomiting developed, and he was admitted to this hospital, where he was found to be dehydrated and acutely ill, and to have an enlarged liver. The response to parenteral fluid therapy was good. During the following ten days there were several episodes of collapse, during which the patient was gray and limp and had gasping respirations and irregular pulse. Parenteral fluids brought prompt recovery from each of these episodes. On one occasion, when Darrow's solution was administered, the patient became rapidly worse, with dehydration, apathy, and cyanosis. After the diagnosis of adrenal insufficiency, the infant was treated with DCA, adrenal cortical extract, and added salt, on which regimen he did well. After a period, to confirm the diagnosis of hypoadrenalism, hormone therapy was discontinued. Five days after withdrawal of therapy, vomiting, fever, weakness, and hepatomegaly developed. At this time, blood sodium was 122.5 mEq. per liter, and chloride, 100.6 mEq. per liter. It was felt that a combination of infection and hormone withdrawal was responsible for this episode. Improvement was prompt when the regimen of hormone and salt was reinstituted. During the following months, the patient grew and developed unusually rapidly; there were several infections accompanied by "Addisonian crises," but each time he responded well to salt, fluid, and hormone therapy. At the age of 14 months, fever, vomiting, sunken eyes, and cyanosis again developed. He was readmitted to the hospital in complete peripheral vascular collapse, and died before therapy could be initiated.

At postmortem examination, the body was that of an obese male infant measuring 84 cm. in length (normal length, 74 cm.). Both adrenals were considerably enlarged. The right weighed 12 Gm., and the left, 14 Gm.; each measured 5 by 4 by 0.7 cm. The outer surfaces were pink-gray, with a greenish tinge in some areas. On cut section, the cortical layer was markedly folded, 2 mm. in thickness, and gray-pink in color. Cut slices immersed in acid silver nitrate solution showed no blackening, indicating a low ascorbic

acid content. The thyroid, pituitary, phallus, and testes were normal on gross examination.

On microscopic examination, the lungs showed moderate interstitial pneumonitis, and there was toxic degeneration of lymphocytes in the splenic follicles.

The adrenal cortex was convoluted and unusually broad; there were multiple small

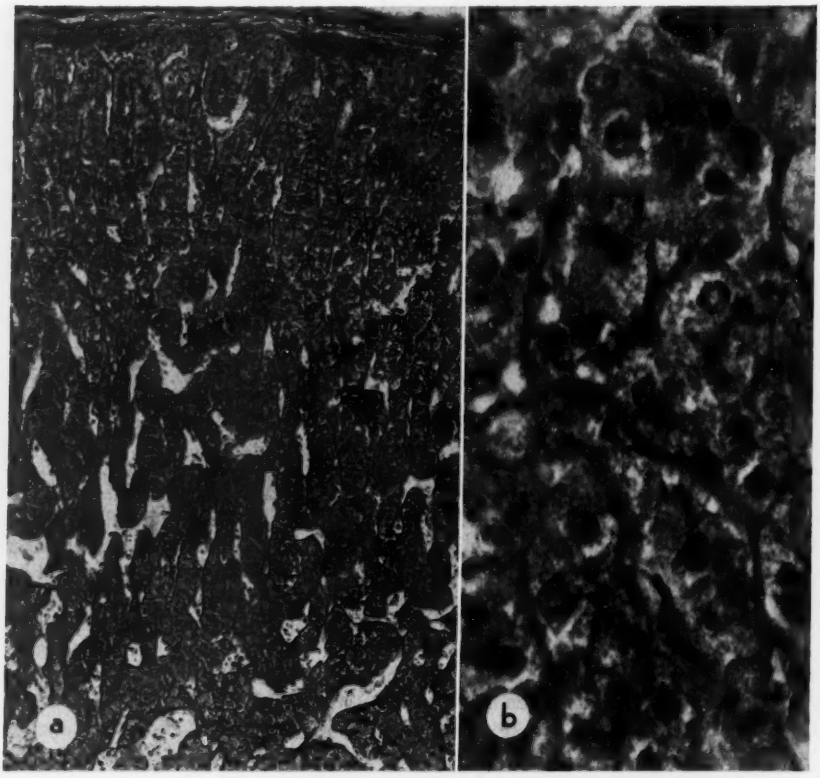

FIG. 1. (Case 1.) *a*. Portion of adrenal cortex showing arrangement of cells into cords, but lack of orientation into zones (hematoxylin and eosin, ×125). *b*. High-power view of adrenal cortical cells. Note round, vesicular, centrally situated nuclei (hematoxylin and eosin, ×750).

extracapsular and subcapsular "adenomas." The cortex was composed of cords of large cells with pale acidophilic granular cytoplasm, many of which contained pigment granules (Fig. 1, *a* and *b*). Except for a thin subcapsular layer of smaller similar cells, there was no apparent division into zones. Sudan 4 stain showed a moderate amount of lipid occurring as multiple small intracellular droplets in the cells of the outer third of the cortex; there was no stainable lipid in the inner two thirds of the gland. The Ashbel-Seligman carbonyl stain (27) gave a faint uniform bluish color. Broster-Vines fuchsin reaction (28) was negative. The medulla was scant but not abnormal.

The testes were immature, with no evidences of spermatogenic activity. No Leydig cells were seen between the tubules. In the region of the hilum and the rete testis, there were many small nodules, as many as five in a section, composed of polygonal cells, smaller than those in the adrenal cortex and having pale, acidophilic, nongranular cytoplasm. These cells were not oriented in cords or zones, and the nodules were not encapsulated (Fig. 2*a*). The nuclei were relatively larger and less regular in shape than those of the adrenal cortical cells. The results with Sudan 4, Ashbel-Seligman, and Broster-Vines stains were negative in these cells. No crystalloids of Reincke were seen. The appearance of the cells in these nodules was typical of that of Leydig cells in normal persons (Fig. 2*b*).

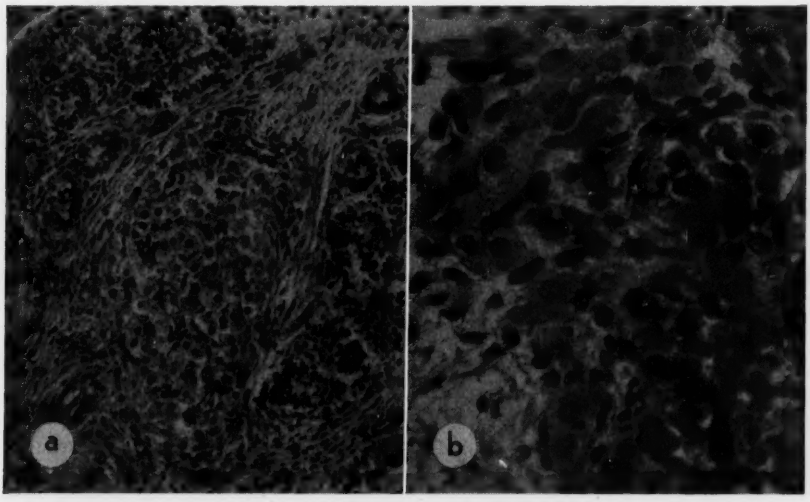

FIG. 2*a*. (Case 1.) Leydig cell nodule in hilar region of testis (hematoxylin and eosin). *b*. High-power view of Leydig cells of normal newborn infant. Note variable shapes of nuclei and cytoplasm (hematoxylin and eosin).

In the pituitary gland, Mallory's aniline blue stain showed the predominant cells to be large chromophobes and basophils, with abundant granular cytoplasm. The eosinophils were relatively sparse, small, and had hyaline, nongranular cytoplasm. No Crooke's cells were seen.

A sibling born ten months after the death of this patient died in another hospital, at the age of 7 weeks, of adrenal insufficiency. At postmortem examination this sibling was found to be a female pseudohermaphrodite with typical adrenal cortical hyperplasia.

Case 2.—This male infant was the product of the sixth pregnancy of a 27-year-old Negro Portuguese mother. His father was a 37-year-old white Portuguese. His birth weight was 8 pounds, 5 ounces. He did well during the neonatal period and was discharged from the hospital at the age of 6 days. He began to vomit after feedings on the first day at home, and continued to do so intermittently for the following three weeks, during which time various feeding regimens were tried.

At the age of 4 weeks he was admitted to another hospital because of dehydration and persistent vomiting. Oral feedings plus supplemental parenteral fluid were insufficient to maintain proper hydration. There were periods of muscle hypotonia which improved when fluid was administered. At the age of 6 weeks he was transferred to this hospital.

When he was admitted, he was poorly developed, considerably undernourished, and dehydrated. He was lethargic, flaccid, and moribund. The phallus and scrotum appeared normal. His weight at this time was 7 pounds, 3 ounces. Two epinephrine tests demonstrated a drop from 137 to 83 eosinophils per cubic millimeter and from 154 to 71 per cubic millimeter, respectively. The blood pH and CO_2 values indicated persistent metabolic acidosis. The serum sodium was 127 mEq. per liter and the chloride, 92 mEq. per liter. He was treated with intravenous fluids, but had several episodes during which the serum sodium and chloride levels dropped precipitously. During such an episode in his

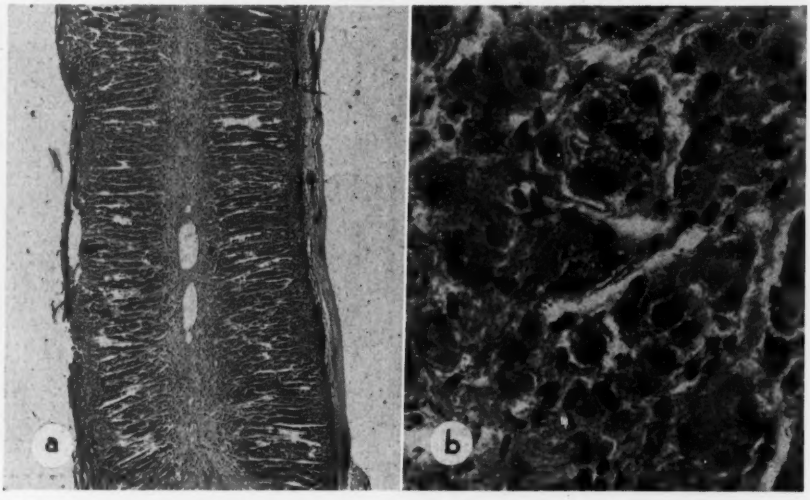

FIG. 3. (Case 2.) *a*. Low-power view of portion of adrenal cortex (hematoxylin and eosin). *b*. High-power view of adrenal cortical cells (hematoxylin and eosin).

fourth week in the hospital, the patient died. Chemical studies on blood drawn immediately post mortem revealed a serum sodium concentration of 126 mEq. per liter and a serum chloride of 89 mEq. per liter.

Postmortem examination revealed a poorly nourished, dehydrated male child. The adrenals were enlarged, the right weighing 6.8 Gm. and the left, 6.5 Gm. Both were greenish gray in color and had an abnormally convoluted surface. On cut surface a cortical zone 2 mm. thick and green-gray in color could be seen. No hemorrhage was present.

A small, firm, encapsulated nodule 3 mm. in diameter was present in the right half of the scrotum, adjacent to the testis. The pituitary and thyroid were grossly normal. The penis was not large.

On microscopic examination, the lungs showed focal atelectasis, emphysema, and chronic pneumonitis; the esophagus showed acute esophagitis, and there was increased hemosiderin deposition in the liver and spleen.

The adrenal cortex was broader than normal, and was composed of cords of moderately large cells with acidophilic granular cytoplasm (Fig. 3, *a* and *b*). Except for a narrow subcapsular layer of cells with paler cytoplasm, there was no evidence of zonation; in particular, no zona reticularis was present. In the center of the gland was a zone composed of the collapsed stroma of the fetal cortex, containing a few degenerating fetal cortical cells. The results with Sudan 4 stain were negative, except in the degenerating

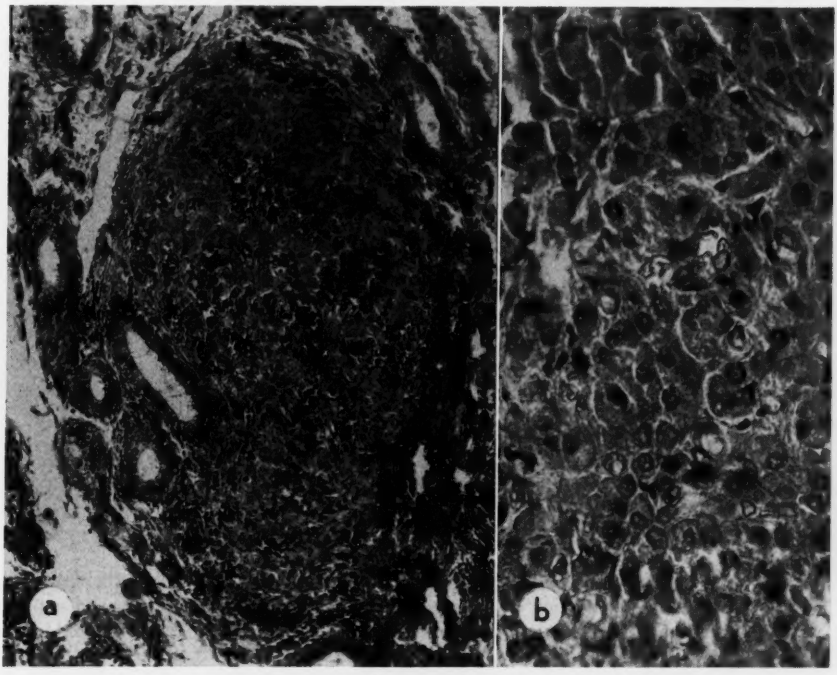

FIG. 4. (Case 2.) *a*. Low-power view of Leydig cell nodule between rete testis and epididymis. Note that nodule is not encapsulated and that cells are not arranged in cords (hematoxylin and eosin). *b*. High-power view of cells of nodule shown in *a* (hematoxylin and eosin).

fetal cortical cells. The Ashbel-Seligman reaction gave a faint, patchy stain, most noticeable in the subcapsular zone and in the residual fetal cortical cells.

The testicular tubules were immature and showed no evidences of spermatogenic activity. No Leydig cells were seen between the tubules. Both testes showed, in the region of the hilum, nonencapsulated nodules of cells, differing from those of the adrenal cortex by their variable polygonal shape, generally darker cytoplasmic staining, and larger, more irregular and vesicular nuclei (Fig. 4, *a* and *b*). No crystalloids of Reincke were seen. As many as four nodules were present in single high-power fields. Many of the nodules clearly surrounded small nerves, and a few cells appeared to penetrate between the nerve fibers (Fig. 5*a*). The cells of these nodules showed no orientation into cords or zones. Adjacent to each rete testis and epididymis was a small encapsulated nodule

of ectopic adrenal cortical tissue, the cells of which were identical with those of the adrenal glands proper, and were arranged in similar cords surrounding a central zone of degenerating fetal cortex (Fig. 5*b*). In phosphotungstic-acid hematoxylin stains, the cells of the ectopic adrenal cortical tissue were bright blue, and those of the hilar nodules, deep purple.

In the pituitary gland, Mallory's aniline blue stain showed many large basophil cells with granular cytoplasm. The Dawson-Friedgood stain (29) showed large numbers of basophils in many clusters; occasionally some of the cells were purple rather than blue,

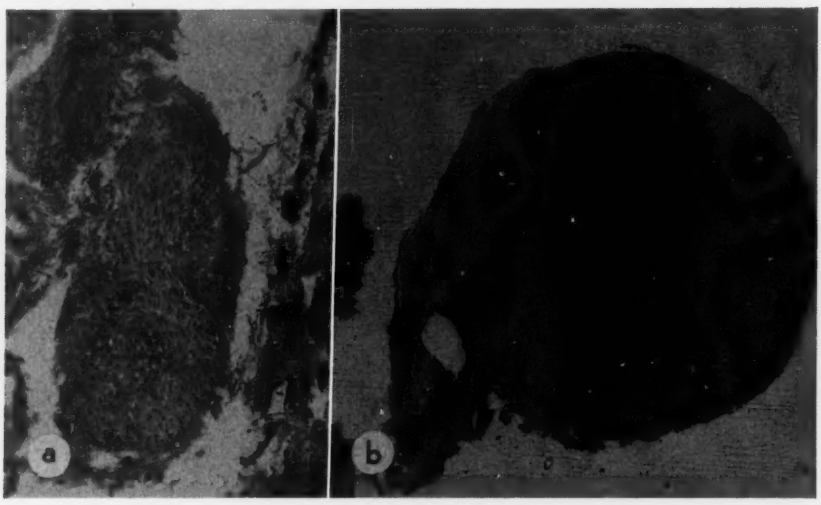

FIG. 5 (Case 2.) *a*. Leydig cell nodule showing relation to nerve fiber (hematoxylin and eosin). *b*. Low-power view of ectopic adrenal nodule showing well formed capsule and arrangement of cells into cords resembling those of the adrenal cortex (hematoxylin and eosin).

and rarely one would be bright red ("carmine cells"). Eosinophils were uniformly small, with clear, nongranular, pale yellow-orange cytoplasm. Gomori's aldehyde-fuchsin (30) stained both the basophils and the "carmine cells" strongly (Fig. 6, *a* and *b*), indicating that the latter are a form of basophil rather than eosinophil, as originally described (29, 31). Periodic acid-leukofuchsin stain showed faint reddish staining of the cytoplasm of all the basophils, suggesting that they contained a mucoprotein-like substance. No Crooke's changes were seen in the basophils.

At the time of this report, 4 siblings of this child are living and have no known endocrine or other disease. One male sibling died two years before this patient was born, at the age of 6 weeks, because of "pneumonia with severe diarrhea." The record of the postmortem examination was not available. Nine siblings of the patient's mother and 10 of the patient's father are living and apparently normal. None is married.

Case 3.—A 5-week-old white male infant was admitted to the hospital because of jaundice which had been present since he was 2 days old. His birth weight had been 9 pounds, 15 ounces. On the fourth day of life he was discharged from the hospital,

mildly jaundiced, with healing omphalitis. The umbilical infection responded at home to therapy with warm compresses and penicillin, but the jaundice persisted.

There was no family history of hemolytic jaundice. One male sibling died at the age of 11 days from "sepsis;" no postmortem examination was performed. Another sibling, a male aged 3 11/12 years is in good health. The mother is Rh positive.

At the age of 2 weeks the infant began to vomit after feedings. The umbilicus was well healed at this time. At the age of 3 weeks, he was admitted to another hospital where he was treated with parenteral fluids and antibiotics. The vomiting decreased in frequency, but diarrhea developed, and the patient was transferred to this hospital.

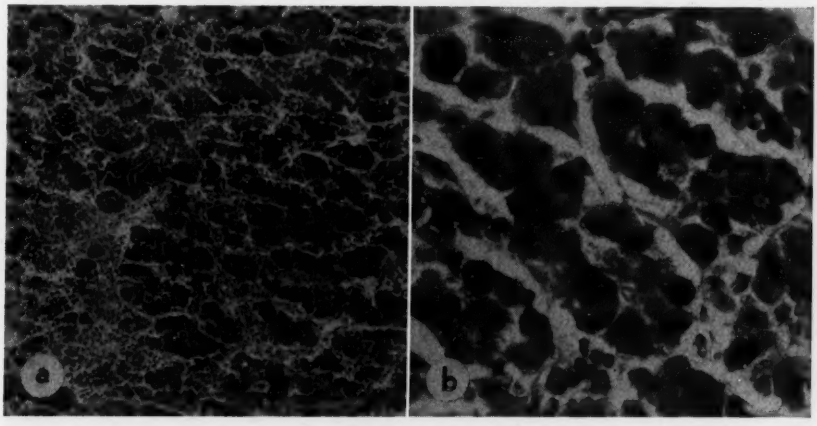

FIG. 6. (Case 2.) *a.* Low-power view of anterior pituitary, showing relative increase in size and number of basophil cells (Gomori's aldehyde-fuchsin). *b.* High-power view of anterior pituitary showing increased number of large basophils with granular cytoplasm (Gomori's aldehyde-fuchsin).

His weight at this time was 7 pounds, 14 ounces. Jaundice was pronounced, and the umbilicus was well healed. The clinical impression was that there was omphalitis with secondary hepatitis. He was treated with parenteral fluids and antibiotics, but died unexpectedly twenty-four hours after admission.

At postmortem examination a lymph node 0.7 cm. in diameter was found compressing the common bile duct. Bile was present in the duct above this point but none was seen below, or in the duodenum. The adrenals were greenish gray, had a distinctly convoluted surface, and together weighed 40 Gm. Cut surface showed a thickened greenish gray cortex and a scant red medulla.

The penis was 2 cm. in length. Grossly, the pituitary, testes and thyroid appeared normal.

On microscopic examination, there were focal pulmonary atelectases, emphysema, edema, and hemorrhage. The liver showed bile stasis, focal extramedullary hematopoiesis and many large multinucleated liver cells.

The adrenals were microscopically identical with those of the patient in Case 2, except that the fetal cortical layer was somewhat larger and contained a greater number of degenerating cells. The Ashbel-Seligman reaction stained only the fetal cortical cells.

The testicular tubules were immature, and showed no evidence of spermatogenic activity. No Leydig cells were seen between the tubules. In the hilar region of both testes there were nonencapsulated nodules, as many as four per section, made up of cells with polygonal shapes, darker-staining cytoplasm and larger, less regular nuclei than those of the adrenal cortex (Fig. 7 *a* and *b*). These were identical with those in the previous cases. One testis also contained, in the same region, a small, round, encapsulated ectopic adrenal, with cells similar to those of the adrenal glands, arranged in cords surrounding a zone of degenerating fetal cortex. Again, the cells of the testicular nodules

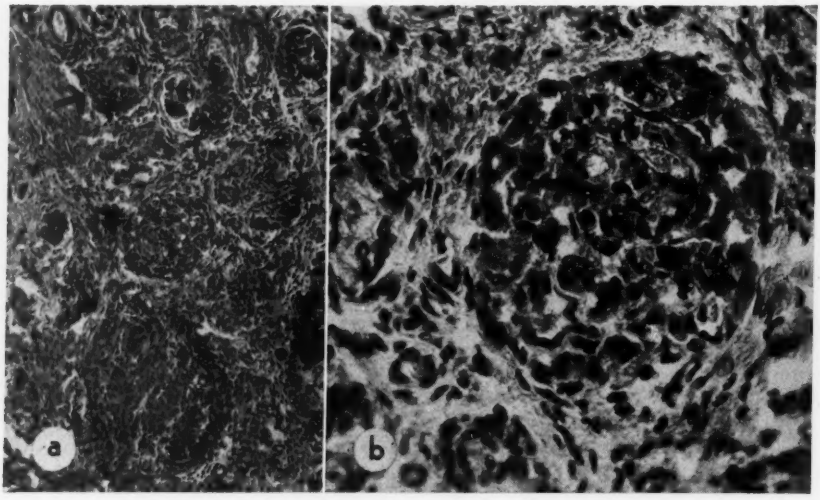

FIG. 7. (Case 3.) *a*. Low-power view of 3 Leydig cell nodules (arrows) between testis and rete testis. Note absence of encapsulation or arrangement into cords (hematoxylin and eosin). *b*. High-power view of Leydig cell nodule (hematoxylin and eosin).

were clearly distinguishable from those of the adrenal glands or the ectopic adrenal tissue.

In the pituitary gland, Mallory's aniline blue stain showed an unusually large number of large basophils with granular cytoplasm. The Dawson-Friedgood stain again showed "carmine cells" with a complete gradation of staining properties ranging into those of the more numerous basophils. The eosinophils were relatively decreased in number, were small, pale, and had hyaline nongranular cytoplasm. Gomori's aldehyde-fuchsin stained both the basophils and the carmine cells strongly, and the periodate-leukofuchsin stain gave a faint pink tinge to the cytoplasm of these same cells. Again, no Crooke's changes were seen.

DISCUSSION

The occurrence in the testes of nodules of cells similar to those which have been described has been reported in 6, and possibly 7, males with familial adrenal cortical hyperplasia. In Table 1 these are listed in order of age, and available data on the size of the testicular nodules are given.

TABLE 1. REPORTED CASES OF LEYDIG CELL PROLIFERATION IN PATIENTS WITH FAMILIAL ADRENAL CORTICAL HYPERPLASIA

Case	Sex	Age	Size of testicular nodules
		Definite cases	
1 (19)	M	2 years	Microscopic
2 (16)	M	2½ years	Not stated
3 (10, 75, 76)	M	3 7/12 years	Left testis, 30 Gm.; right, 8 Gm.; both homogeneous dark brown
4 (9, 22)	M	6 years	Reddish central nodules, 1 cm. in diameter
5 (5, 20, 77, 78)	M	11–13 years	Biopsy only
6 (1)	M	20 years	Testes 3 by 1 cm., with central red-brown nodules, 2 by 1 cm.
		*Doubtful cases**	
7 (21)	M	6 weeks	Microscopic
8 (23)†	F	6½ weeks	Microscopic
9 (24)	F	5 months	Microscopic
10 (25)‡	F	9 2/12 years	Microscopic
11 (4)	F	79 years	Microscopic
12§	F	?	?

* All of the cases in females were doubtful.
† Fibiger's Case 3.
‡ Seckel's Case 6.
§ This case was quoted by Sternberg (60).

Since all 6 patients with definite testicular lesions were older than any of the 3 we have described, in whom testicular nodules were not grossly visible, and since there is a tendency for the nodules to be larger in the older patients, it seems probable that the testicular lesions in our patients represent an early stage of the more advanced testicular lesions described by others.

The evidence presented by previous authors, that these testicular nod-

ules are composed of adrenal cortical cells, is based on the gross and microscopic similarity of the nodules to the enlarged adrenals (1, 10), the presence in many patients (including our Cases 2 and 3) of enlarged ectopic adrenal tissue in other sites such as the broad ligament (4, 32, 33), the absence of crystalloids of Reincke in the cells forming the nodules (1, 20), the absence of Leydig cells elsewhere in the involved testes (20), and the similarity of the involutionary changes in the adrenals and testes after administration of testosterone (20). The similarity in gross appearance of these nodules to adrenal cortex is merely the result of the presence of lipid and pigment in the cells of both, and has been noted (34) in well-defined cases of Leydig cell hyperplasia. As has been described previously, although the cells of the testicular nodules and those of the hyperplastic adrenal cortices of these patients generally are similar, they are easily distinguishable in specimens obtained from a given patient at a given time. In one reported instance (1), as well as in our Cases 2 and 3, both ectopic adrenal tissue and abnormal testicular tissue were present and easily distinguishable in the same patient.

Furthermore, as mentioned previously, ectopic adrenal nodules show well defined capsules and arrangement of the cells in cords, whereas these testicular nodules do not. Crystalloids of Reincke are not ordinarily found in Leydig cells before puberty (35), and are rare in well defined Leydig cell tumors (1, 36–38). Nodular Leydig cell hyperplasia occurs with varying frequency in a number of conditions, the majority, and perhaps all, of which are associated with increased secretion of pituitary gonadotropin. Examples of these are: prolonged estrogen administrat on (39–42); male pseudohermaphrodism (hypospadias, cryptorchism, and sometimes gynecomastia) (43–48); cryptorchism (49, 50); old age (34, 36, 49); gigantism (Fig. 8); hepatic cirrhosis (26); various other serious illnesses, particularly tuberculosis (49, 51, 52); and possibly also the syndrome of testicular tubular hyalinization (53). Finally, it is well known that Leydig cells involute in response to administration of androgen (54, 55). In addition to these points, the predominantly hilar location of the nodules suggests that seen in the normal Leydig cell hyperplasia of the newborn, as well as in other reported instances of Leydig cell hyperplasia (56) and the relation of the nodules to nerve fibers is typical of both Leydig cells and ovarian hilar cells (57–60). The known rarity of ectopic adrenal tissue within the testis (61, 62) supports this conclusion that these testicular nodules are composed of Leydig cells.

In view of the preponderance of reported instances of familial adrenal cortical hyperplasia in females (3), a surprisingly small number of cases suggestive of hilar cell hyperplasia of the ovary exist. These are listed in the second portion of Table 1. We have been unable to detect hilar cell

hyperplasia in routine sections of the ovaries of 5 newborn female pseudohermaphrodites, one the sibling of the patient described in Case 1. A distinct difference between males and females with this disease may exist in this regard. There are, however, as is discussed in the introduction, other major differences between males and females with this syndrome, probably the most important being the relative absence of Addisonian symptoms in, and the considerably longer average life span of, affected females.

As was mentioned in the introduction, the etiology and pathogenesis of

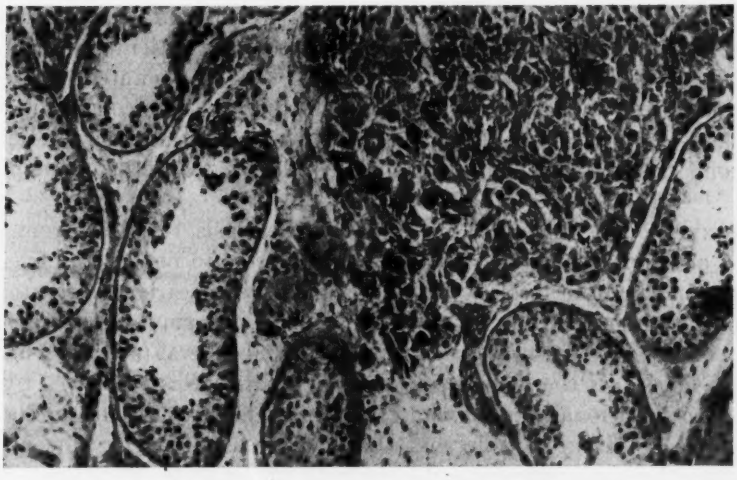

FIG. 8. Portion of Leydig cell nodule in hilar region of testis of 12-year-old patient with gigantism. Note lack of encapsulation or of arrangement into cords, and irregular shape of cells (hematoxylin and eosin, ×200).

familial adrenal cortical hyperplasia are still uncertain. It seems to be well established that the causative factor becomes operative early in intrauterine life, since the genital tract malformations found in affected females represent an arrest of differentiation at this stage of development. Albright and his co-workers (18) in 1941, proposed that the disease was the result of overproduction of pituitary luteinizing hormone (LH). It is well known that LH stimulates Leydig cells (63), and there is considerable inferential evidence that it also stimulates adrenal androgen production (18, 64, 65), but not the other functions of the adrenal cortex. More recently, Bartter and his co-workers (15) postulated that the disease is the result of a primary inability of the adrenal cortex to synthesize S (sugar)-hormone, with the resultant stimulation of pituitary corticotropic hormone production, leading to adrenal cortical hyperplasia and production of excess adrenal

androgen. Unfortunately, no LH determinations on patients with this disease appear to have been performed, and only one instance of elevated ACTH production has been reported (15). Since the production of excess adrenal androgen in the presence of a normal pituitary would seem to be more likely to depress than to lead to hyperplasia of Leydig cells, the presence of this finding in the testes of the patients described in this paper and those described in the literature would appear to support the first of these two possible explanations.

Although the conclusion is not universally accepted (29, 31, 66), the bulk of evidence suggests that LH, as well as ACTH and FSH, is secreted by the basophil cells of the pituitary (66–74). In the patients we have described, there was definite basophil predominance in the anterior lobes of the pituitaries. This evidence also supports the tentative conclusion that the basic cause of familial adrenal cortical hyperplasia is oversecretion of hormone, possibly luteinizing hormone, by the basophil cells of the pituitary.

In experimental animals, Leydig cell hyperplasia resulting from sustained anterior pituitary stimulation can progress to benign and even to malignant tumor formation (39–42). Suggestive cases have occurred in human beings in the form of Leydig cell tumors of cryptorchid testes. In at least 2 reported instances, these tumors were bilateral (45, 50). There is also evidence that the sequence of Leydig cell hyperplasia followed by benign, and occasionally malignant, tumor development occurs in elderly dogs (34, 36). It is possible that the development of benign neoplastic properties by the hyperplastic Leydig cells in the testes of patients with familial adrenal cortical hyperplasia, accounts for the fact that in 2 of the reported cases of Leydig cell hyperplasia (10, 20), one testis became much larger than the other. To date, however, possibly because of the short life span of affected males, no case suggestive of malignant transformation in the testes of these patients has been reported.

SUMMARY

The clinical features and pertinent gross and microscopic pathologic findings in 3 male infants with familial (congenital) adrenal cortical hyperplasia have been reported. All 3 had nodular hyperplasia of cells, considered to be Leydig cells, in the region of the testicular hilum and rete testis. These nodules differ from those of ectopic adrenal tissue by the nuclear and cytologic features of the cells, their lack of a capsule, the lack of arrangement of their cells into cords, and by their relation to nerve fibers. Other cases of nodular hyperplasia of similar cells in patients with this disease have been reported in the literature. The evidence suggests that these previously reported cases of "ectopic adrenal tissue within the testis"

or of "bilateral adrenal cell tumor of the testis" actually were also instances of nodular Leydig cell hyperplasia. The anterior pituitaries of all 3 patients contained evidence of increased secretory activity of the basophils and decreased activity of the eosinophils, supporting the conclusion that the basic cause of both the Leydig cell and the adrenal cortical hyperplasia in these patients is oversecretion of tropic hormone, possibly luteinizing hormone, by the anterior pituitary gland. It is possible that, under certain conditions, the Leydig cell hyperplasia in these patients could progress to benign or malignant tumor formation.

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THE FAILURE OF WATER DIURESIS IN ADDISON'S DISEASE*

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A CONSIDERABLE number of studies of renal function in adrenocortical insufficiency have suggested that lack of prompt diuresis after administration of water is a consequence of increased tubular reabsorption. The results of the present studies indicate that, under the experimental conditions we have followed, the failure of rapid diuresis when water is administered to patients with Addison's disease is due, in part at least, to a decrease in the rate of glomerular filtration.

PROCEDURE

Eleven subjects were studied: 6 of them, all men, were proved to have Addison's disease, and 5 served as controls; of these, 4 were men and 1 was a woman.

The diagnosis of Addison's disease was established by the typical history of marked tiredness and fatigue, loss of weight, lack of appetite, digestive troubles and darkening of the skin. The physical examination showed deep and typical pigmentation of skin and mucous membranes, low blood pressure in all but 1 patient (Case 1), and evidence of inactive pulmonary tuberculosis in 3 (Cases 2, 3 and 5). The result of the "water test" was positive in 4 cases and negative in 2 (Cases 1 and 6). The result of the therapeutic test with desoxycorticosterone acetate (DCA), 2 to 3 mg. daily, for twelve to fourteen days, was positive in all the patients, with significant gain of weight and increase of blood pressure, both of which again decreased after the treatment had been discontinued (1). The 6 patients who had Addison's disease required administration of DCA either by intramuscular injection or by implantation of pellets, without which all of them at one time or another suffered from crises of adrenal insufficiency of variable intensity; Patients 2 and 3 both died as a consequence of such crises. In every case the evolution of the disease confirmed the diagnosis.

The control subjects were patients with the following diagnoses: Patient

Received for publication April 10, 1951.

* These studies were performed in a laboratory specially designed and maintained by Laboratorios Andrómaco S.A., Buenos Aires, Argentina.

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7, syphilitic meningoradiculitis; Patient 8, chronic fatigue; Patient 9, idiopathic eunuchoidism; Patient 10, essential hypertension; Patient 11 (female) rheumatoid arthritis. None presented gross renal malfunction, as judged by the common laboratory criteria.

Mannitol clearances were determined by the single-injection method (2, 3); 12.5 Gm. of mannitol dissolved in 50 ml. of water were injected intravenously after the solution had been warmed to body temperature. We were aware of the fact that the continuous infusion method would have been more in accord with the general practice, notwithstanding that previous reports (3) have stated that clearances of mannitol are constant at any plasma level. The main reason why we preferred the single-injection method was that this seemed to us more tolerable to patients as frail as patients with Addison's disease are, especially considering that determinations had to be repeated in each subject.

All the tests were performed under basal conditions with the patients lying down, fourteen hours after the last meal. Each patient was submitted to two determinations of mannitol clearance: during the first one no water was given by mouth, whereas the second test was performed immediately after the patient had ingested the second of two doses of water. This test, which was performed one week after the first, was conducted in the following way: the urine of the previous night, from 11 p.m. to 7 a.m., was collected; at 7:15 a.m. blood was drawn from an arm vein and mixed with heparin, as were all other blood samples, and immediately afterwards the first dose of 15 ml. of water per kilogram of body weight was administered by mouth. Two hours later, a second sample of blood was obtained, and while mannitol was injected intravenously within approximately ten minutes, the patients again ingested the same amount of water, with the aid of a rubber tube. Eighteen to twenty-five minutes after the injection of mannitol had been completed, the collections of urine were started, by means of an indwelling catheter; after each collection of urine, the bladder was washed with 20 ml. of warm distilled water, followed by the injection of 20 cc. of air to help complete collection of fluid. In most cases collections were made for four periods of thirty minutes each; at the beginning and at the end of every period, blood was withdrawn from the cubital vein. With the values of mannitol in the different blood samples, a graph was constructed on semilogarithmic paper, in which the concentrations of plasma mannitol were plotted as ordinates and time as abscissas. These graphs approximated a straight line with the desirable accuracy (3). The plasma values of mannitol concentration were thus calculated from the graphs at the midpoint of every period of collection of urine. The corresponding clearance was calculated according to the formula UV/P, in which U represents the concentration of mannitol in the urine, P its concentration in plasma, and V the volume of urine per minute.

TABLE 1. PATIENTS WITH ADDISON'S DISEASE

Case	Weight, Kg.	Height, meters	With or without water	Diuresis, ml./min.	Mannitol clearance, ml./min.	Water reabsorption		Sodium			
								Filtered, mEq./min.	Excreted in urine μEq./min.	Reabsorbed	
						ml./min.	% of filtrate			mEq./min.	% of filtrate
1	66	1.75	Without	2.51	100.7	98.1	97.6	14.60	323	14.27	97.7
			With	10.94	78.2	68.5	83.3	10.64	174	10.47	98.3
2	47	1.59	Without	1.11	61.7	60.6	98.3	8.72	82	8.64	99.2
			With	1.48	52.3	50.9	97.2	7.36	114	7.25	98.5
3	58.5	1.69	Without	2.93	62.7	60.9	97.0	8.33	163	8.16	98.1
			With	3.76	55.0	51.0	92.8	7.68	250	7.43	96.8
4	63.0	1.64	Without	2.35	68.1	65.9	96.7	8.72	280	8.44	97.0
			With	1.65	60.4	58.6	97.2	7.36	156	7.20	98.3
5	47.0	1.57	Without	1.55	106.7	105.4	98.6	12.84	137	12.70	98.9
			With	2.73	79.7	76.6	96.6	10.01	205	9.81	98.0
6	68.5	1.72	Without	1.99	106.6	104.5	98.0	14.10	187	13.91	98.7
			With	12.54	86.2	74.2	86.1	10.91	182	10.73	98.3
CONTROLS											
7	72.0	1.68	Without	2.02	104.9	103.0	98.2	15.26	205	15.06	98.7
			With	13.0	99.7	87.7	88.5	14.48	193	14.26	98.7
8	74.0	1.73	Without	2.12	110.8	110.1	98.2	14.82	376	14.44	97.5
			With	10.7	115.2	103.2	89.6	16.50	353	16.15	97.9
9	65.5	1.86	Without	2.79	120.4	117.7	97.7	16.50	431	16.07	97.4
			With	14.02	132.2	119.4	90.2	18.52	599	17.92	96.7
10	77.0	1.69	Without	2.25	102.5	100.4	97.9	14.31	388	13.92	97.2
			With	9.40	116.2	103.2	92.7	15.70	290	15.41	98.1
11	51.5	1.56	Without	1.89	96.0	94.1	98.0	14.42	223	14.20	98.5
			With	6.56	94.7	88.7	93.8	13.40	166	13.23	98.7

None of the subjects presented signs of intolerance to the injection of mannitol, except for very mild chills in a few instances. During the tests in no instance was a lowering of blood pressure observed, either in the control subjects or in patients with Addison's disease.

In patients who were being treated with DCA or extra sodium salts such treatments were omitted at least five days prior to the tests. Thus the tests were conducted on patients with essentially untreated Addison's disease. All subjects were in good condition at the time the tests were made, with no signs of dehydration in any case.

METHODS OF ANALYSIS

For the determination of mannitol the method of Silberstein and associates (4) was employed, using deproteinized plasma according to Somogyi, following the procedure of Smith and associates (5). The same deproteinized plasma, using aliquots of 5 ml., was utilized for duplicate determinations of mannitol, which was titrated in neutral medium, as well as for determinations of glucose according to the method of Shaffer, Hartmann and Somogyi (6). The same technic was followed for urine, after it had been verified that neither glucose nor proteins were present. Sodium in plasma and urine was determined by the gravimetric method of Barber and Kolthoff (7), with uranyl zinc acetate (8). Urinary phosphates were eliminated with calcium hydroxide.

RESULTS

The data for rate of urine flow, mannitol clearance and sodium excretion, together with the calculated values for water and sodium reabsorption, are shown in Table 1. In this table the mean values only are given.

Diuresis.—During the double-load water test, the urine volume per minute in the control subjects was high during the two hours that followed administration of the second dose of water. The total urine volume during these two hours was higher than the overnight (11 p.m.–7 a.m.) urine volume in every control subject (Table 2).

Four of the patients having Addison's disease (Cases 2, 3, 4 and 5), on the other hand, had a low urine volume following the second ingestion of water; in 3 of these, the total two-hour urine volume was lower than the overnight volume, while in the fourth (Case 5), it was slightly higher. The 2 other patients with Addison's disease (Cases 1 and 6) showed high urine volumes per minute, which fell within the range of the controls; the total urine volumes for these two hours were decidedly higher than the corresponding overnight volumes.

Glomerular filtration rate (mannitol clearance).—During the test without water ingestion, the glomerular filtration rates (GFR) of patients with Addison's disease, compared with the values of the controls, were lower in 3 cases (Cases 2, 3 and 4), and similar in the other 3 cases. After ingestion

of water, GFR was lower in all the patients with Addison's disease than in the controls.

In each separate case, if the values of GFR during the test without water are compared with GFR values during the water test, the following results are noticeable:

Three of the 5 controls (Cases 7, 8 and 11) presented an increase or a decrease not exceeding 5 per cent, whereas in the remaining 2 (Cases 9 and 10) there was an increase of GFR of more than 5 per cent after the

TABLE 2. WATER DIURESIS IN MILLILITERS DURING THE NIGHT (11 P.M.–7 A.M.) AND FOR THE TWO HOURS FOLLOWING THE SECOND INGESTION OF WATER: PATIENTS WITH ADDISON'S DISEASE AND CONTROLS

Addison's disease			Controls		
Case	Night 11 P.M.–7 A.M.	2 hours after 2nd water load	Case	Night 11 P.M.–7 A.M.	2 hours after 2nd water load
1	322	1,577	7	312	1,849
2	290	181	8	455	1,344
3	673	478	9	760	1,791
4	1,170	223	10	400	1,439
5	198	322	11	555	1,005
6	265	1,476			

water load. In the patients with Addison's disease, on the contrary, a constant decrease of GFR after the double ingestion of water was observed, which was in every instance more marked than the maximal fluctuations presented by the control group.

Water reabsorption (difference between GFR and urine excreted).—If the values of the first test, without water administration, are compared with those of the second test, after two doses of water, the following differences can be noticed:

In three of the 5 controls (Cases 7, 8 and 11), the water reabsorption, expressed in milliliters per minute, was decreased after the double water load, whereas in the remaining 2 (Cases 9 and 10) a slight increase, probably not significant, resulted. Calculated as percentage of the values of GFR, the reabsorption was decreased in all the controls during the water test.

In the patients with Addison's disease, the reabsorption values, when

expressed as milliliters per minute, were markedly decreased in all cases after the double ingestion of water, even more than in the controls. This decrease of the fluid reabsorbed after the ingestion of water, when considered *proportionally to the GFR*, was clearly more accentuated in those cases (1 and 6) which presented high urine volume than in those with low urine volume. In Case 3, during the water test the diuresis was slight, notwithstanding the marked decrease of water reabsorption, even when considered as percentage of the GFR.

Plasma sodium.—The values were generally lower in patients with Addison's disease than in the controls. In neither of the two groups were there evident changes during the water test (Fig. 1).

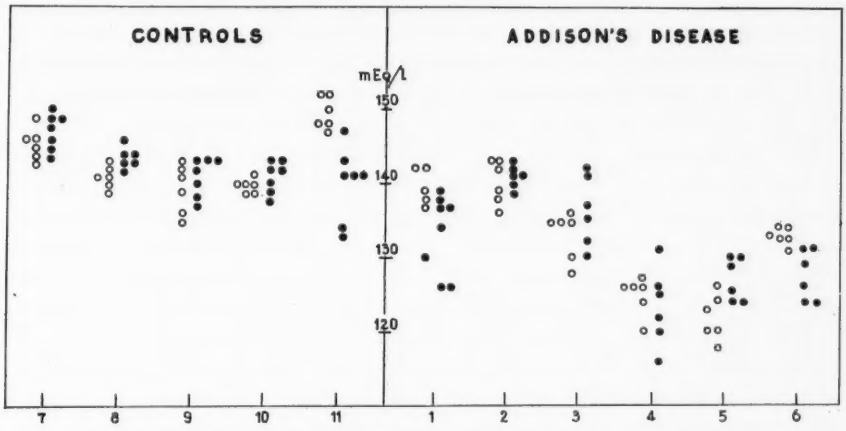

FIG. 1. Plasma sodium in milliequivalents per liter, in patients with Addison's disease and controls. White dots: during the test without water ingestion. Solid dots: during the test with water load.

Excretion of sodium.—In the group of patients having Addison's disease the total urinary sodium during the two hours that followed the second administration of water did not present constant or significant changes, if compared with that excreted during the two hours in the first test, without water.

If the total amount of sodium excreted during the two hours after the ingestion of water is compared with the total sodium of the overnight urine (11 p.m.–7 a.m.), the ratio (Na 11 p.m.–7 a.m./Na two hours after water) tends to be higher in the patients with Addison's disease than in the controls (Table 3). This seems to indicate that patients with Addison's disease who receive water tend in general to excrete less sodium than the control subjects, when compared with the sodium excreted in the overnight urine.

Sodium filtration.—After the double water load, the controls did not show any constant variation in sodium filtered. On the other hand, in patients with Addison's disease the sodium filtration, expressed in milliequivalents per minute, was decreased in all instances, reflecting the changes in GFR during the water test.

Sodium reabsorption.—During the double water load test, no constant changes were present in the controls, whereas in the patients with Addison's disease the reabsorption of sodium, expressed as milliequivalents per

TABLE 3. TOTAL SODIUM EXCRETED IN THE NIGHT URINE (11 P.M.–7 A.M.) AND DURING THE TWO HOURS FOLLOWING THE SECOND INGESTION OF WATER, AND THE RATIO OF THESE QUANTITIES: PATIENTS WITH ADDISON'S DISEASE AND CONTROLS

Addison's disease				Controls			
Case	Total sodium, mEq.			Case	Total sodium, mEq.		
	11 P.M.–7 A.M.	2 hours after water	Ratio		11 P.M.–7 A.M.	2 hours after water	Ratio
1	62.0	20.6	3.00	7	55.0	23.7	2.32
2	55.4	15.8	3.50	8	70.2	46.4	1.51
3	110.4	32.9	3.35	9	93.0	72.9	1.28
4	58.0	17.7	3.27	10	48.0	36.5	1.31
5	40.9	23.1	1.77	11	59.6	24.3	2.45
6	47.5	21.5	2.21				

minute, was lower in all cases than the values during the test without water. These changes in the patients with Addison's disease paralleled those of water reabsorption, expressed in milliliters per minute.

Reabsorption of sodium as percentage of the sodium filtered, during the tests without or with water, did not present constant changes either in patients with Addison's disease or in the control group.

COMMENT

The concept that lack of rapid diuresis in adrenocortical insufficiency (9, 10, 11) depends fundamentally on an increased tubular reabsorption rate (TRR) is derived from a generalization of the mechanism to which the normal control of water diuresis is attributed (12, 13). This concept is

supported by a speculation on the reciprocal action between adrenocortical and post-pituitary antidiuretic hormones (ADH) (14, 15), which assumes that the two hormones display an antagonistic activity in the regulation of water diuresis. Thus, it is supposed that in the absence of adrenocortical secretion, ADH is more active, because it is secreted in larger quantities, or because it is less inactivated by the liver, or finally because of an increased sensitivity during adrenal insufficiency (16–19). It is noticeable that this increase of sensitivity to ADH, which is in fact very marked in adrenal insufficiency (17)—even with minute doses (20)—does not seem to be in accord with the existence of a high rate of circulating ADH since, in general, organisms are less sensitive to small quantities of a hormone when the endogenous production is high than when it is low.

In any case, several facts do not fit into the scheme of an antagonistic and complementary action between adrenocortical and post-pituitary hormones in the regulation of water excretion by the kidneys. Among these are the experiments which give evidence of faulty water diuresis in adrenalectomized (21) as well as in totally hypophysectomized animals (18) in the proved absence of any demonstrable ADH. It must be remembered, however, that after total hypophysectomy, besides the alterations in adrenal and post-pituitary function, other factors play a role, such as the absence of growth hormone (22) and of those influences exerted through the thyroid and gonads. Failure of rapid water diuresis has likewise been found in human hypopituitarism (23, 24, 25). All these facts strengthen the belief that in cortical insufficiency there may intervene other factors which would act independently of ADH, and the influence of which would be even more important in the failure of water diuresis. A very complete and detailed discussion of these subjects may be found in the review by Gaunt, Birnie and Eversole (21). An interesting fact is that observed by Boss, Birnie and Gaunt (26) in adrenalectomized rats which were given different doses of water; these authors found that, whereas with a moderate water load the fundamental trouble preventing water diuresis is excessive TRR, with high doses of water approximating 18 per cent of body weight, reduction of GFR intervenes at the same time that symptoms of water intoxication become evident; nevertheless these authors found that the diuresis is proportionally more reduced than GFR.

The results of the present studies on patients with Addison's disease show that under the experimental conditions followed, the double water load produces marked decrease in GFR. This depression of GFR after water ingestion is accompanied by a constant reduction, though usually less accentuated, of the total TRR values calculated as milliliters per minute. This fact does not seem to be in harmony with a presumptive marked activity of post-pituitary ADH. Also it must be emphasized that during

the two hours that follow the double water load, the total sodium excreted in urine, as compared with the sodium excreted in the overnight urine, was in general lower in patients with Addison's disease than in the controls. A lower excretion of sodium after the ingestion of water in patients with Addison's disease, when compared with those without Addison's disease had previously been found by Reforzo-Membrives, Power and Kepler (23), after the patients had been treated with high doses of sodium salts. Since post-pituitary ADH seems to facilitate the excretion of sodium and chloride (15, 24 and 27–34) these results do not lend support to the idea of a great activity of ADH, precisely in the moment when patients with Addison's disease fail to present abundant diuresis.

The reduction of TRR, as calculated in milliliters per minute, after water ingestion in the patients with Addison's disease studied, seems to constitute a sort of compensatory mechanism which, when sufficiently great, is able to overcome the decrease of GFR, with a resulting high diuresis (Cases 1 and 6). In other patients with Addison's disease, the reduction of the TRR is not sufficiently great to compensate for the lowered GFR, and diuresis is impaired. If the values of TRR are considered proportionally to the GFR, it may be seen that in some cases the ratio TRR/GFR$\times$100, during the water test, may decrease enough to compensate easily for the decrease of GFR; this may be the mechanism through which some patients with Addison's disease have abundant diuresis, thus giving a negative result of the water test (35). In other patients, on the contrary, in spite of a lowering of TRR after water ingestion, in milliliters per minute, the percentage of fluid reabsorbed proportionally to the GFR continues as high or almost as high as during the test without water ingestion. Finally, the TRR as percentage of GFR may decrease after the ingestion of water, reaching values within the range of the control patients; yet the GFR may also have fallen to such a low level that extremely poor diuresis results.

It appears to be evident that multiple factors are able to modify the renal response to water administration in adrenal insufficiency, and therefore in analyzing and comparing the experiments one with another, these facts must be borne in mind before general conclusions can be drawn. Especially important seem to be:

1. The animal species. In fact the multiple and valuable experimental studies of Gaunt and associates, as well as those of many others (21, 26, 34 and 36–41), indicate that in some species, particularly in the rat, the principal factor responsible for the lack of rapid diuresis after adrenalectomy is increased TRR; the role played by a lowering of GFR in the failure of water diuresis becomes effective only when the water administration reaches very high levels—about 18 per cent of body weight—which produce evident signs of water intoxication (26). On the other hand, in our studies

of patients having Addison's disease, the total amount of water administered reached 3 per cent of body weight, and in no instance were there any signs of intolerance or any change in blood pressure. The experiments of Boss, Birnie and Gaunt (26) thus point to the necessity of taking into account in each case the quantity of water administered considering that the mechanisms involved may vary accordingly.

2. Attention must be paid to prior treatment, since it has been demonstrated that sodium salts and DCA influence renal function in adrenal insufficiency as well as in normal organisms (15, 36, 38, 39 and 41–45). The appreciation of this fact offers some difficulties, for the two substances seem to produce different effects, whether administered together or separately. Thus Braun-Menendez (46) has observed that in rats the administration of DCA, even in high dosage, does not produce changes in the water turnover if sodium chloride is absent from the diet. Reforzo-Membrives, Power and Kepler (23) have observed that in patients with Addison's disease the administration of large amounts of sodium salts does not restore rapid water diuresis.

3. It is necessary to take into account the fact that in patients with Addison's disease the alterations in renal function in the absence of water load (40, 44 and 47–50) do not seem to be exactly the same, or at least do not reach the same intensity, as during water load.

The present studies support the view that in the faulty water diuresis of adrenal insufficiency there intervenes as a fundamental factor a decrease of GFR. An excessive TRR was not found in any case, for even when considered proportionally to the lowered GFR, the TRR of water was insufficiently inhibited only in some of the patients with Addison's disease. Therefore the present results cannot be added to the series of experiments in favor of an excessive activity of post-pituitary ADH; in any case, if the latter exists, it does not seem to be either indispensable or fundamental for the mechanism of faulty water diuresis in patients with Addison's disease.

The observed depression of GFR raises the question whether the sudden administration of abundant water to organisms with adrenal insufficiency does produce circulatory changes with deviation of intrarenal blood flow, similar to the ones described by Trueta and associates (51). It is interesting to note that in our studies on patients with Addison's disease, at the time when GFR suffered a marked decrease, no lowering of the blood pressure was observed, nor did the typical symptoms of peripheral circulatory failure appear; this makes it seem less probable that the failure of rapid diuresis could be due to ischemic changes, similar to those described by Van Slyke (52) during the first phase of shock. In the light of the experiments of Trueta and associates it seems advisable to re-examine the prac-

tice of considering the renal functions of GFR and TRR as independent processes. In this respect it is appropriate to recall the statement made by Smith (12), that it is impossible, with the data available, to assert definitely that variations in GFR do not intervene in the regulation of water excretion, though, he added, there are good reasons to believe that urine flow is especially controlled through the changes in TRR. It appears that the idea that GFR may also contribute to the regulatory mechanism of urine excretion deserves some attention; it may well be that, under certain conditions, changes of GFR play a part in this mechanism, especially during rapid adjustments of diuresis. It has been observed by Brod and Sirota (53) that in the rabbit GFR parallels the decrease of urinary flow under the influence of emotional stimuli. Equally interesting is the fact observed in men by Talso, Crosley and Clarke (54), that the immersion of a foot in iced water produces a decrease of both GFR and effective plasma flow.

In considering hormonal influences on intrarenal blood flow, one must think of the experimental facts demonstrated by Wakim, Herrick, Baldes and Mann (55), which indicate that pitressin under certain conditions is able to determine changes that Trueta and associates interpreted as a vasoconstriction of the renal cortex with deviation of the blood flow through the medullary shunt, and consequent decrease of GFR. It appears worth while to determine the possible influence of adrenal cortical hormones on all these processes.

SUMMARY

Mannitol clearance tests, employing the single-injection method, were performed on 6 patients with untreated Addison's disease and on 5 controls. In each subject two different tests were carried out: one without water administration and another after the ingestion of a double water load. The following results were observed:

1. After the double water load, diuresis was low in 4 of the 6 patients with Addison's disease.

2. The values of GFR (glomerular filtration rate as measured by mannitol clearance) were lower in 3 patients with Addison's disease than in the controls during the test without water, and in all 6 patients with Addison's disease the values of GFR were lower than in the controls during the test with double water load.

3. In patients with Addison's disease, GFR during the water test was markedly and constantly decreased in comparison with the test without water ingestion.

4. The decrease of GFR in patients with Addison's disease during the water test was accompanied by a lowering of the TRR (tubular reabsorp-

tion rate) values as calculated in milliliters per minute. This reduction of TRR in some cases was sufficiently accentuated to permit abundant diuresis, in spite of low GFR; in other cases, the decrease of TRR after the ingestion of water was less accentuated, especially if calculated as percentage of GFR, with consequent low urine volumes.

5. The total sodium excreted in the urine within two hours after the ingestion of water tends to be lower in patients with Addison's disease than in the controls, when compared with total sodium excretion during the previous night.

It is concluded that a decrease of GFR plays a role in the failure of rapid diuresis when water is administered to patients with Addison's disease.

Acknowledgment

We should like to express our gratitude to Dr. M. H. Power, who, together with the late Dr. E. J. Kepler, first aroused our interest in this subject, and who has been kind enough to revise the manuscript.

Addendum

After submission of this paper, we have noted the results of H. Ludemann, L. Q. Rais and H. Wirz (Filtration rate and water diuresis in the dog, *Am. J. Physiol.* **166:** 416–420, 1951). These authors state that, in the dog, the fraction of filtered water excreted during water diuresis increases significantly with increasing filtration rate.

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CHANGES IN THE CIRCULATING LEUCOCYTES FOLLOWING ELECTRICALLY INDUCED CONVULSIONS IN MAN*†

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THE striking clinical improvement in some psychiatric patients following convulsive therapy has led to much research and theorizing concerning the mechanisms essential to this clinical change (1–4). Since the introduction of pharmaceutical convulsants by von Meduna (5, 6) and Cerletti's (7, 8) extension to human subjects of his work on electroshock in dogs and pigs, many physiologic studies have been carried out. During this same interval, knowledge of the physiologic significance of the adrenal cortex has increased greatly (9–12). It has been discovered that changes in adrenocortical activity are followed by a variety of changes in the number and distribution of the circulating leucocytes (13–18). This observation has caused a renewed interest in the influence of electroshock on the blood picture, and the work of earlier investigators (19–22) has been extended and, in general, confirmed by work done in the past few years (23–27).

The present paper is yet another contribution to these studies of the effect of convulsive therapy on the blood picture. It was prompted by our interest, similar to that of several others (23, 25–27) in acquiring evidence about the activation of the adrenal cortex by electroconvulsive therapy (ECT), as suggested by Hemphill *et al.* (28) and by Hoagland *et al.* (29).

Our preliminary impressions from this study have been reported in outline previously (30).

MATERIAL AND METHODS

Subjects

From among the patients of the Allan Memorial Institute who were receiving ECT, 57 convulsions were studied in 15 subjects. These patients were unselected, except that those with clinical contraindications to venipuncture were avoided, and those whose ward behavior indicated that

Received for publication June 12, 1951.

* Read by title at the Annual Meeting of the Association for the Study of Internal Secretions, Chicago, Illinois, June 18 and 19, 1948.

† This investigation was carried out under a grant from the National Research Council of Canada.

they might be cooperative were preferred. The group included 6 women and 9 men; except for 1 male of 19 years, their ages ranged from 30 to 60 years. In 14 cases depression was the main clinical feature; in 1 patient the diagnosis was schizophrenia.

Treatment

In this institute all electroshock treatments are preceded routinely by intravenous sodium amytal. In 9 subjects omission of this sedative was arranged; in the remaining subjects such omission seemed clinically unwise. We therefore have studies on 19 treatments in 9 patients without sodium amytal, and on 38 treatments in 15 patients with prior sodium amytal. The number of treatments studied per patient varied from 1 to 7, 4 being the number most frequently investigated. The investigation usually began with the patient's first treatment.

For these treatments the classic type of biphasic stimulator (Rahm Instruments, Inc.) was used on 30 occasions and the Liberson brief-stimulus apparatus (Offner Electronics, Inc.) on 27.

Procedure

Venous blood was taken shortly before treatment, and again one, two, four and six hours later. In patients receiving sodium amytal intravenously the blood sample was taken just prior to this injection; if, as in a few instances, the handling of treatments was such that some delay occurred between the injection of sodium amytal and the ECT, then the first sample preceded the treatment by this interval. It was not always possible to secure all samples on all patients.

Techniques

The venous blood was drawn with minimum stasis and mixed with the least possible amount of dry oxalate. Smears and counts were made promptly; if some delay was inevitable, the blood was placed in a refrigerator. Smears were made on cover slips, and stained with Wright's stain. A differential count of 200 cells was made on each of the slips; hence 400 stained cells were counted for each sample; in a few cases more cells were counted. The direct total leucocyte count was made with a 1:20 dilution of Türck's solution; the cells were enumerated in four Neubauer chambers. Direct eosinophil counts were made by the modified method of Dunger as described by Forsham *et al.* (31). Eight Fuchs-Rosenthal chambers were used for the enumeration, so that in a total leucocyte count of 10,000 with 2 per cent eosinophils, a total of over 250 different eosinophils would be seen and enumerated.

RESULTS

In presenting the changes in the counts of neutrophilic, lymphocytic and eosinophilic leucocytes after ECT, the treatments have been grouped in four ways: (a) all 57 treatments of all 15 patients, both *with and without* sodium amytal; (b) the 38 treatments of the 15 patients *with* prior sodium amytal; (c) the 19 treatments of the 9 patients *without* sodium amytal; and (d) the 22 treatments of the same 9 patients as in (c), but *with* prior sodium amytal. In the graphs, (Figs. 1, 2 and 3) group (b) has been omitted

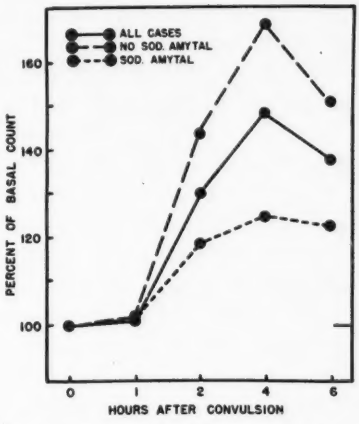

FIG. 1. Effect of ECT on neutrophil counts

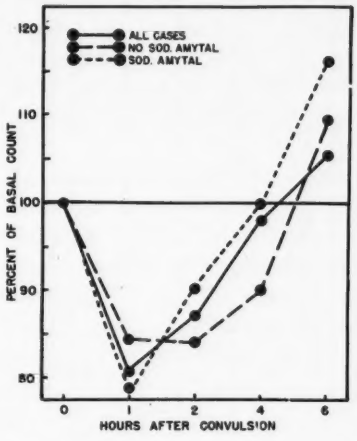

FIG. 2. Effect of ECT on lymphocyte counts.

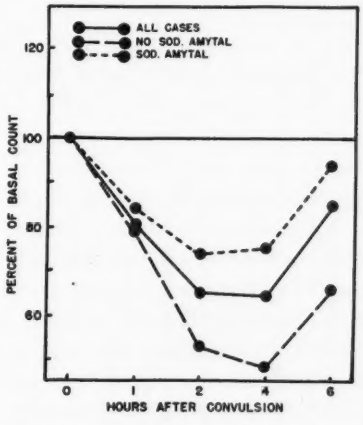

FIG. 3. Effect of ECT on eosinophil counts.

TABLE 1

	Time interval after convulsion															
	1 Hour				2 Hours				4 Hours				6 Hours			
	Subgroups of patients*				Subgroups of patients*				Subgroups of patients*				Subgroups of patients*			
	a	b	c	d	a	b	c	d	a	b	c	d	a	b	c	d
Neutrophils																
Mean *increase* from basal count (cells per cu. mm.)	−15	−192	39	−93	1,232	936	1,916	789	2,004	1,368	3,042	880	1,519	1,292	1,827	1,050
No. of treatments	57	38	19	22	53	37	16	22	50	31	19	19	44	26	18	15
P	.1	.2	.9	.7	.001	.02	.001	.06	.001	.01	.001	.1	.001	.02	.001	.1
P[1]							.06				.04				.3	
Lymphocytes																
Mean *decrease* from basal count (cells per cu. mm.)	578	607	521	574	455	442	484	380	207	133	332	332	−225	−358	−33	−342
No. of treatments	57	38	19	22	53	37	16	22	51	32	19	20	44	26	18	15
P	.001	.001	.01	.001	.001	.01	.01	.05	.1	.4	.1	.2	.1	.4	.7	.3
Eosinophils																
Mean *decrease* from basal count (cells per cu. mm.)	44	40	53	50	67	52	101	60	76	50	121	61	40	14	86	18
No. of treatments	57	38	19	22	53	37	16	22	51	32	19	20	50	31	19	18
P	.001	.001	.001	.001	.001	.001	.001	.001	.001	.001	.001	.001	.001	.3	.01	.5
P[1]							.05				.02				.05	

* Subgroups of patients:

a. 15 patients, all treatments, *with and without* sodium amytal.
b. 15 patients, treatments *with* sodium amytal.
c. 9 patients, treatments *without* sodium amytal.
d. 9 patients, treatments *with* sodium amytal.

because of the close similarity of the results in this group to those in group (d).

The results of the statistical assessment have been expressed in two ways: 1) a comparison has been made between the pre-treatment and post-treatment counts after each interval for each type of leucocyte; and 2) a comparison between the changes in these counts following the treatments with sodium amytal, and those without it, in the same group of patients. The probability that any difference shown by the first comparison is due to chance has been designated P, and such probability for the second comparison, P^1. Both P and P^1 were obtained by the use of the *t*-test (32); since P refers to the average of the difference between pre-treatment and post-treatment counts, in the same patient and for the same shock treatment, the *t*-test applied was that for matched pairs. For P^1 no satisfactory pairing was possible.

In Table 1, we have listed the *mean change* from the pre-treatment count in the number of circulating neutrophils, lymphocytes, and eosinophils, at the specified intervals of one, two, four and six hours following the convulsion. As it was not always possible to secure all the blood samples after every treatment, the number of treatments used in calculating the means have also been listed. The figures deal graphically with the same basic data, except for the omission of group (b), as noted above. Here, the general trends are made more clearly apparent by expressing each count as a percentage of the corresponding pre-treatment count, and then plotting the average of such percentages against time. It may be noted that the scale for the interval of zero to two hours is twice as great as for the interval of two to six hours, merely as a matter of convenience in presentation.

In the following description of our results, we use the expressions "significant" and "highly significant" in their usual sense, to denote a value for P and for P^1 of .05 or less, and of 0.01 or less, respectively.

Neutrophils

1. At one hour, there is no definite change, though the average percentage shows a slight increase; at two hours, there is a definite increase, which continues at the fourth hour (when it reaches an average of 3,042 for those treated without sodium amytal); by the sixth hour, there is some decrease from the fourth hour, but the count is still well above the basal level. This increase is highly significant in most groups at two, four and six hours.

2. At four hours the difference between the average increase of 3,042 with sodium amytal and that of 880 without, in the same 9 cases, is significant; at two hours the difference between the average increase of 1,916 and that of 789 does not quite meet the usual standard of significance.

Lymphocytes

1. In all groups, the maximum decrease in lymphocytes occurs at one hour (an average of 578 for all treatments), and in all groups it is highly significant; at two hours, the decrease is less, but is still highly significant in most groups; by four hours, the counts have increased towards the basal count and become scattered so that the decrease is no longer significant.

2. At six hours, the lymphocyte count is above the basal count in all groups, but this increase is not significant.

3. The average difference for the 9 patients treated with and without sodium amytal is not significantly different for the two types of treatment, at any interval, and therefore the P^1 values for this difference have been omitted from the table.

Eosinophils

1. The counts decrease at one hour, and further at two hours; at four hours, they still show a slightly greater decrease for treatments without sodium amytal. After all three intervals, the average difference from the basal count is highly significant.

2. By six hours, the counts are still low, but have returned toward the basal value, so that only in the total series, and in the group treated without sodium amytal are the counts still significantly below the basal count.

3. At two, four and six hours, the average difference between the counts in patients treated with sodium amytal, and the counts in the same patients treated without sodium amytal, is significant.

COMMENT

Any study of blood count changes inevitably has a degree of uncertainty and requires much work because the probable error of such counts is relatively high (33–45), in addition to other sources of inaccuracy in technique and variability in the subject. Hence the validity of any conclusion based on a few counts unsupported by critical statistical analysis depends upon support from similar results in more comprehensive studies. By now, there is sufficient agreement among several rather extensive studies (21, 23–27) of the effect of convulsive therapy on the blood picture, to reinforce the general conclusions.

In examining the reports of changes in circulating leucocytes after convulsive therapy, one notes that there is considerable variation in the length of the post-convulsive interval over which the studies were made. In general, the studies fall into two groups: those (19–22, 24, 25) concerned with the changes that occur promptly or during the first hour after the

convulsion, and those (23, 25–27) reporting the changes during the first four to six hours, or even longer, after the convulsion. Most of the latter group of studies are more recent than the former, and their findings are essentially the same as those we have reported here. It is interesting to note that both Fattovich (46, 47) and Horn (48) likewise reported an increase in neutrophils, with a decrease in lymphocytes and eosinophils, as a delayed effect after pharmaceutically induced convulsions.

The similarity of these later blood cell changes to those ascribed to increased activity of the adrenal cortex is very striking (15, 16, 18), and indeed it would be strange if such muscular activity and such hypoxemia as occur with ECT were not followed by marked increase in adrenocortical activity, for such stresses are known to stimulate the adrenal cortex (49–52). However, the evidence of Mikkelsen and Hutchens (23) that 5 cases of unconsciousness without convulsions following the usual electrical stimulation (the so-called "petit mal" type of response) showed the same type and degree of late change in the lymphocyte count, suggests that the adrenal cortex becomes active without the severe muscular exertion, and probably with much less degree of hypoxemia than occurs after most ECT. This suggestion receives further support from the work of Hoagland *et al.* (53) on the activation of the adrenal cortex by nonconvulsive electroshock treatment.

The work of Hume (54) on the role of the hypothalamus in the activation of the adrenal cortex and that of Lorimer *et al.* (55) on the potential gradients within the cranium during an ECT-like setup indicate that the change in the electric field across the hypothalamic nuclei may initiate the physiologic sequence which eventually results in these later changes in leucocyte counts. Hence we may attribute these changes to activation of the adrenal cortex by the electric potential *per se*, rather than to the muscular activity and anoxia.

As it seems unlikely that human subjects with discrete provable anatomic lesions involving parts of the hypothalamic adrenocortical system will come under treatment with ECT, further elucidation of this aspect of the problem must come from animal studies.

It would seem we must look elsewhere than to the adrenal cortex for an explanation of the changes in the leucocyte picture occurring during the first post-convulsive hour. These early post-ECT changes include: (a) fluctuations in neutrophil and total white cell counts during the first fifteen minutes after the convulsion (the scatter of the average increase (19–22, 24, 25) is so wide that, when statistically reported (21), the usual standard of significance has not been satisfied) followed by a return of the total leucocyte count to about the pre-treatment level within twenty to

forty minutes of the convulsion; and (b) increases in the lymphocytes, averaging over 75 per cent above the pre-shock level, reaching a peak within ten minutes, and returning to the basal count within thirty to sixty minutes (19, 21, 22, 24, 25).

That endogenous epinephrine may cause these early post-ECT changes in the blood picture is suggested by the work of Parsons *et al.* (25), who showed similar changes in 14 subjects, particularly in the lymphocytes, thirty minutes after the injection of 0.01 mg. of epinephrine per kilo of body weight. Felici (19) and Delay and Soulairac (56), however, report that "petit mal" responses are not followed by these early changes in the blood counts, and yet such nonconvulsive responses produce an increase in blood sugar (57), indicating sympathetic stimulation with epinephrine production. Indeed, without epinephrine production the later effects of adrenocortical activation would be unlikely (58). It would seem, therefore, that if endogenous epinephrine causes the early post-ECT leucocyte changes, it must be produced in larger quantity or for a longer period after "grand mal" responses than after "petit mal" responses. Alternatively, some other difference between these two types of response accounts for the difference in the early post-ECT blood picture. Perhaps the muscular activity *per se* is this other difference, for the changes in the neutrophilic and lymphocytic counts in the early post-shock interval are similar to those reported following spontaneous convulsions (59, 60) or accompanying muscular exercise (61, 62, 63). Though changes in hemoconcentration and plasma protein level occur briefly after both ECT (1, 64) and exercise (65) they are relatively much less than the changes in leucocyte counts. Such activity, however, is believed (37) to open up the capillaries in the muscles, lungs and liver, thus releasing the leucocytes sequestrated in such reservoirs. The contraction and squeezing of the spleen probably makes only a slight addition (37), whereas the increased flow of lymph from limbs and viscera (62, 66) floods the blood stream with lymphocytes.

CONCLUSIONS

1. Following each electroconvulsive treatment, there are conspicuous changes in the blood picture during the next few hours:
   a) increase in neutrophils,
   b) decrease in eosinophils,
   c) decrease in lymphocytes.
2. These changes resemble those due to activation of the adrenal cortex by exogenous ACTH, or by stress.
3. The change, particularly in neutrophils and eosinophils, is less if the shock is preceded by intravenous sodium amytal.

SUMMARY

Counts of the neutrophils, lymphocytes, and eosinophils have been made before, and at one, two, four and six hours after 57 electroconvulsive treatments in 15 patients. Nineteen treatments have been studied in 9 of these patients without the use of intravenous sodium amytal. There was an increase in neutrophils and a decrease in lymphocytes and eosinophils similar to those noted after injections of ACTH. The changes were greater when sodium amytal was not used.

The problem is discussed of the extent to which activation of the adrenal cortex is due to the excessive muscular activity and hypoxemia accompanying the convulsion, or, more directly, to the electrical stimulation of the head.

Studies by other workers indicate a leucocytosis and lymphocytosis within a few minutes of the convulsion; and "petit mal" responses are reported to exhibit the later lymphocytopenia without the earlier leucocytosis and lymphocytosis. These observations suggest the greater importance of the electrical stimulation in the activation of the adrenal cortex.

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THE GROWTH AND HISTOLOGIC CHANGES OF HUMAN THYROIDAL TUMORS TRANSPLANTED INTO THE ANTERIOR CHAMBER OF THE EYES OF GUINEA PIGS*†

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THE survival and growth of a variety of human malignant tumors after transplantation into the anterior chamber of the guinea pig's eye has been demonstrated by Greene and his associates (1–4). According to these authors the behavior of transplanted tumors serves as a means of distinguishing between benign and malignant lesions. The malignant lesions were reported to survive and grow; the benign lesions and normal adult tissue were rather promptly absorbed.

From the histologic point of view, some tumors which arise from the thyroid gland are quite obviously malignant; others are benign. There are, however, some which defy certain identification as to their benign or malignant state. Some of these lesions appear to resemble normal thyroidal tissue but are found in aberrant locations. Some embryonic thyroidal tumors initially are considered benign, but subsequently have been proved to be malignant. Still others histologically consist of a papillary configuration and metastasize after many years.

The objects of this investigation were as follows: 1) to observe the growth potentialities of benign and malignant tumors of the thyroid after transplantation to the anterior chamber of the guinea pig's eye; 2) to compare the results of the transplantation with the morphologic interpretation of the fixed microscopic preparations of the original tumor; and 3) to explore the possiblities of changes in the histologic character of these tumors after transplantation.

Samples of human thyroidal tumors were retained under sterile condi-

Received for publication June 18, 1951.

* Read at the Annual Meeting of the American Goiter Association, Columbus, Ohio, May 24, 1951.

This article will be included in the bound volume of the "Transactions of the American Goiter Association" published by Charles C Thomas, Publisher, which will be available for sale early in 1952.

† Aided by a Grant-in-Aid from the American Cancer Society.

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tions at the time of operation. By the use of prompt frozen-section technique, an attempt was made to find those tumors in which a subsequent morphologic diagnosis might be difficult. The tumors were transplanted into the eyes of normal white albino guinea pigs which weighed between 300 and 500 grams. Both male and female hosts were used, but the animals were separated to avoid the influences of pregnancy. All of the animals were given a normal diet of rabbit chow and lettuce and so far as could be determined, none suffered from a deficiency in thyroidal function.

Under sterile conditions a small fragment of tumor was inserted into the anterior chamber of the anesthetized eye according to a technique described by Dobyns and Lennon (5). All transplantations were performed within four hours after the removal of the tissue from the patient. Great emphasis was placed on the care with which the transplantation was made, because trauma to the lens or iris usually resulted in a failure of the growth of the transplant. All animals were marked for identification. From time to time diagrams were made to illustrate the size and position of the tumor in the eye.

Twenty-three thyroidal tumors and controls of 3 normal thyroids were each placed in from 3 to 19 eyes. A total of 218 eyes in 124 animals were observed for periods of from 18 to 827 days. In many instances a histologic examination was made of the eyes or of a fragment of tissue removed from the eyes at the time that the animals were sacrificed or died.

Since Greene (4) has pointed out that occasionally malignant tumors lie dormant in the eye for a period of time before they begin to grow, an arbitrary period of ninety days was chosen after which the survival of the tumor was regarded as significant. Although this arbitrary interval was chosen, many of the transplants were allowed to remain in the eye for more than a year.

From the results that will be described, it will be seen that some of the malignant tumors grew, and some showed a tendency to differentiate. However, there was some discrepancy between the morphologic diagnosis of malignancy and the diagnosis based on the behavior of the tumor after transplantation.

The results of the observations on the behavior of these transplanted tumors may be classified as follows: 1) disappeared promptly; 2) remained dormant for a considerable period of time, then grew and occupied most of the anterior chamber and later regressed; 3) remained dormant for long periods without evidence of growth, but subsequently found to consist of viable tumor cells; 4) remained dormant for long periods without growth, and subsequently found to have been replaced by connective tissue or calcification; and 5) appeared to have been absorbed but later reappeared.

Most of the control tissue (normal human thyroid) was rather promptly

absorbed. Some of these transplants, however, remained for as long as ninety days and in 4 instances a few acini could still be identified in the connective tissue ninety-three days after transplantation. Although thyroidal tissue may have been identified, the cells appeared rather shrunken, suggesting that further survival was at least moderately limited.

Most of the highly malignant tumors survived and grew in some of the animals; however, there was always a latent period of several months before growth began. Minute blood vessels appeared on the surface of the transplants preceding the period of growth (Fig. 1). Transplants of some

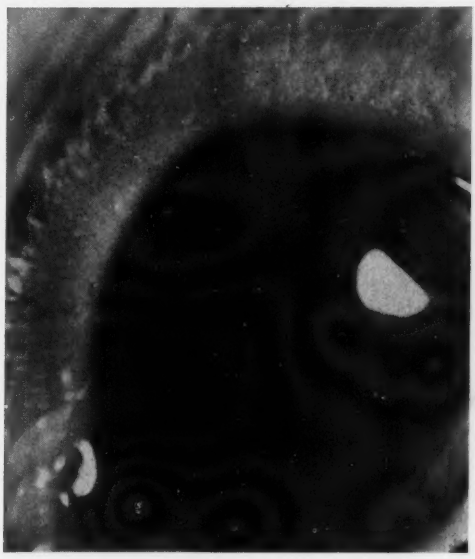

FIG. 1. A tumor growing in the anterior chamber of the guinea pig's eye. Blood vessels may be seen on the surface of the growing tumor. (Courtesy of *Ann. Surg.* Dobyns and Lennon (7).)

of these tumors grew until they filled the anterior chamber and appeared to distend the eye. By the time this period of maximal growth had been reached, evidence of spontaneous necrosis had begun. It is of interest that although these tumors were highly malignant, their rate of growth was much slower than that described for malignant lesions of other organs by Greene and Lund (2).

Among 12 transplants of hyperplastic adenomas (Fig. 2) from patients with thyrotoxicosis, 3 transplants survived ninety days, but microscopic examination revealed that tumor cells had been replaced by connective tissue. Eight transplants from a Hürthle cell adenoma (Fig. 3) were absorbed within ninety days.

The behavior of tranplants from 2 primitive fetal adenomas drew special attention. Both of these lesions were classified as benign, according to morphologic criteria. Seven transplants of one (Fig. 4A) of these histo-

FIG. 2 (above). A hyperplastic adenoma with acini containing colloid. This tumor did not grow in the guinea pig's eye and only questionably survived 90 days.

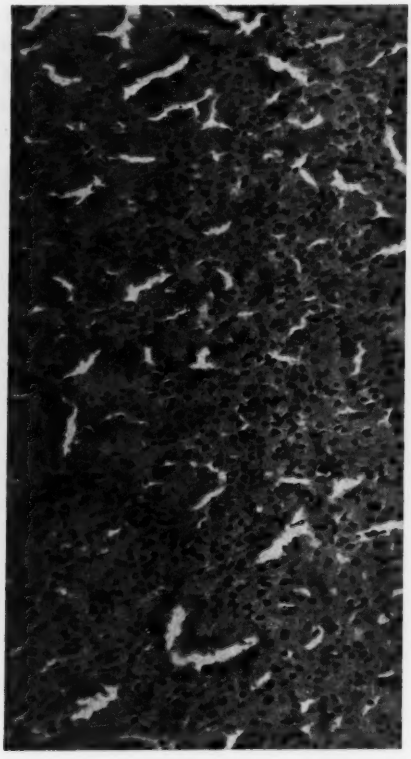

FIG. 3 (right). Hürthle cell adenoma—a solid, cellular tumor with very rare acini. This tumor was not considered malignant according to morphologic criteria. Its behavior on transplantation did not suggest malignancy. (Courtesy of *Ann. Surg.* Dobyns and Lennon (7).)

logically benign tumors survived grossly in the eye for more than ninety days but showed no evidence of growth; however, histologic preparations made from 2 of the transplants after 424 days revealed the presence of viable tumor cells (Fig. 4B). Of the transplants from the other morphologically benign tumor (Fig. 5A) there were 2 which remained longer than ninety days, and 3 others which disappeared and then reappeared. The

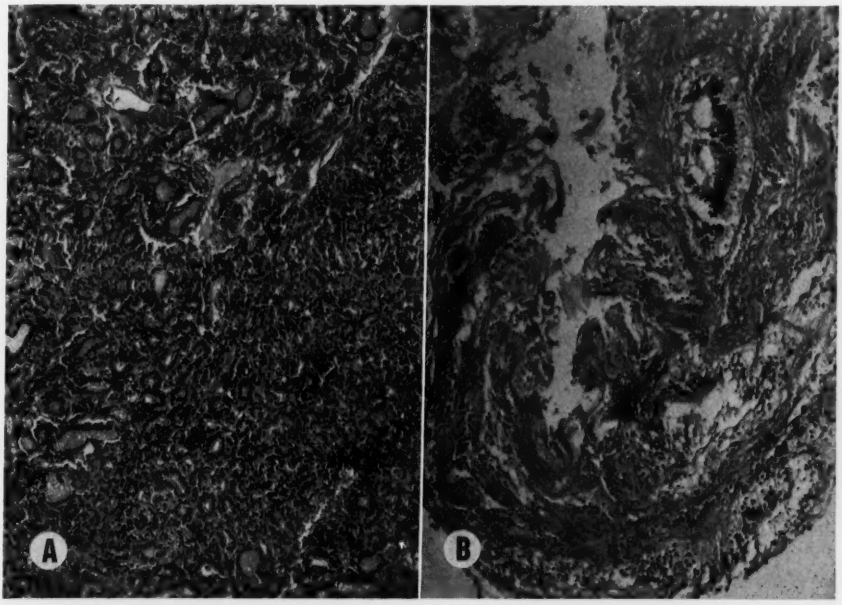

FIG. 4. Benign fetal adenoma with areas of minute acini. (Courtesy of *Ann. Surg* Dobyns and Lennon (7).)

A. The primary tumor. Seven transplants made from this tumor survived more than 90 days.

B. A histologic preparation of a transplant which remained 424 days in the anterior chamber of the guinea pig's eye. This photograph represents a tuft of connective tissue which formed about the transplant. The cavity suggests that there has been some loss of substance of the transplant; however, viable tumor cells forming acini can be seen. On the basis of morphologic criteria, this tumor was regarded as benign.

histologic preparations of one of these transplants (294 days) contained plasma cells mixed with other cells (Fig. 5B), an observation which led to uncertainty in making a definite diagnosis of surviving tumor, although the general cellular pattern resembled the original tumor. According to Greene (4), any transplant which is composed of viable tumor cells after a long period of time should be classified as malignant even though gross evidence of growth has not occurred. The definite histologic evidence of survival 424 days after transplantation of one tumor, and the evidence of slight growth (disappearance followed by the reappearance) of 3 transplants of the other tumor suggested that a diagnosis of malignancy should have been made, although six pathologists unanimously and independently

regarded these tumors as benign on the basis of their morphologic appearance.

One to 7 transplants of each of 5 different papillary adenocarcinomas survived grossly for at least ninety days. Slight growth occurred in transplants from 4 of the 5 tumors; however, in only 1 instance in which histologic study was made were surviving tumor cells found (Fig. 6, A and B).

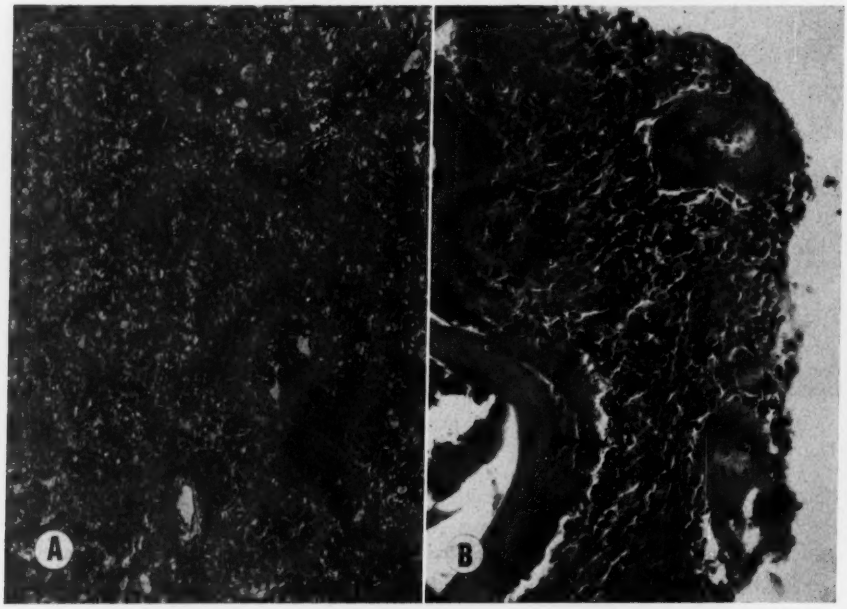

FIG. 5. A benign fetal denoma. (Courtesy of *Ann. Surg.* Dobyns and Lennon (7).)

A. The primary tumor. Two transplants of this tumor remained in the eye for more than 90 days and 3 others disappeared and then reappeared.

B. Tissue removed from the anterior chamber of an eye 294 days after transplantation. The presence of plasma cells mixed with other cells led to some uncertainty in making a definite diagnosis of surviving tumor.

This transplant had been present in the eye for 233 days, and many of the others had been allowed to remain considerably longer. If the period of observation had been shortened and the histologic preparations had been made somewhat sooner, in all probability, viable tumor cells would have been found in some of the surviving transplants which appeared to grow slightly.

Calcification was found in several types of transplanted tumors but was found most commonly in the papillary adenocarcinomas. Although the

frequency of calcification in this type of lesion may have been a coincidence, it will be recalled that papillary adenocarcinomas tend to form microscopic calcification in clinical subjects.

Numerous transplants of metastatic tissue from 2 patients with follicular adenocarcinoma remained unabsorbed for a long period of time. One of these showed slight growth and was successfully retransplanted. An-

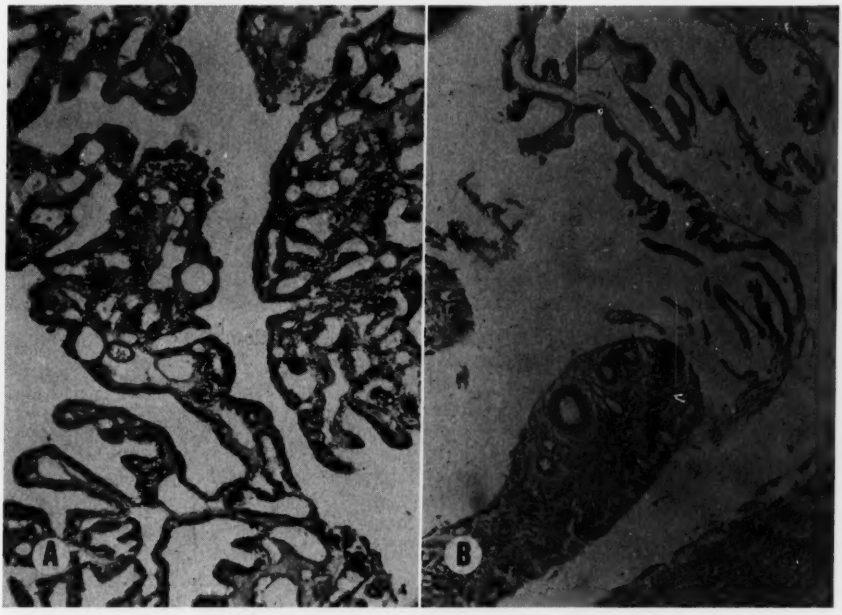

FIG. 6. Mixed papillary and follicular adenocarcinoma. (Courtesy of *Ann. Surg.* Dobyns and Lennon (7).)

A. Primary tumor, a discrete encapsulated nodule in the thyroid.

B. This transplant had disappeared in the eye after 139 days. By 233 days, it had reappeared.

other contained surviving tumor cells 272 days after transplantation (Fig. 7 A and B), but had shown no evidence of growth.

After a period of survival in the guinea pig's eye, several of the tumors showed a tendency toward differentiation (Fig. 8 A and B). A comparison between the histologic pattern of the transplant and of the primary tumor (in the immediate area from which the transplant had been taken) suggested that the degree of differentiation found in the transplant had not existed in the primary tumor.

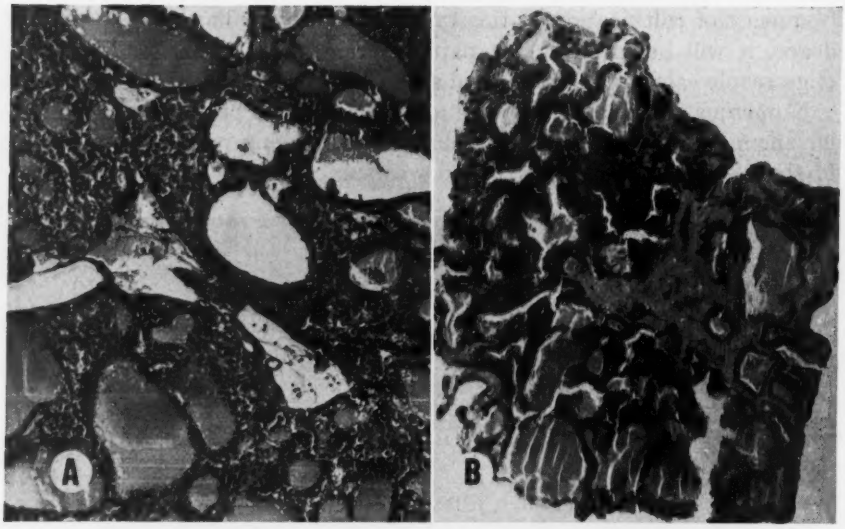

FIG. 7. See opposite page for description.

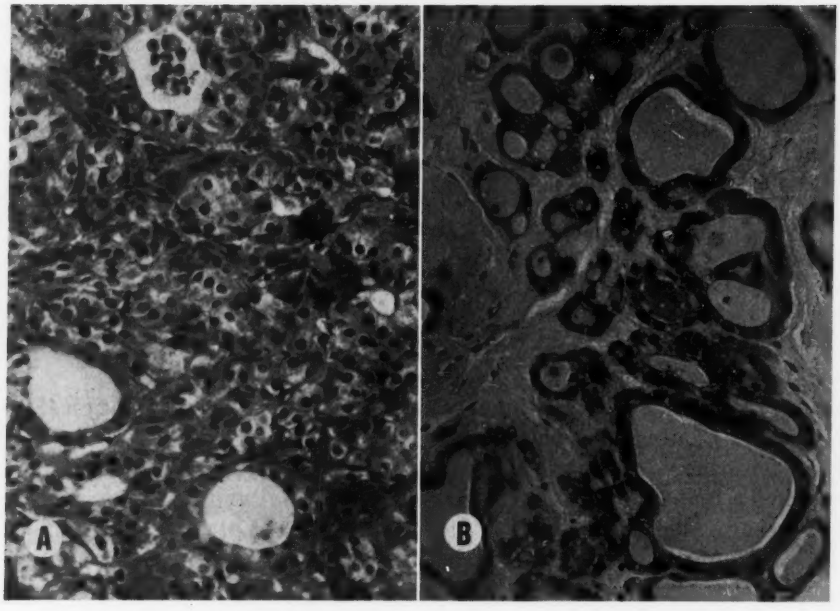

FIG. 8. See opposite page for description.

Because of the differentiation that was found to be taking place in transplants, observations were made to determine whether these lesions would take up radioactive iodine in their new environment. After the transplant had grown to appreciable size, the thyroid of the host was totally removed

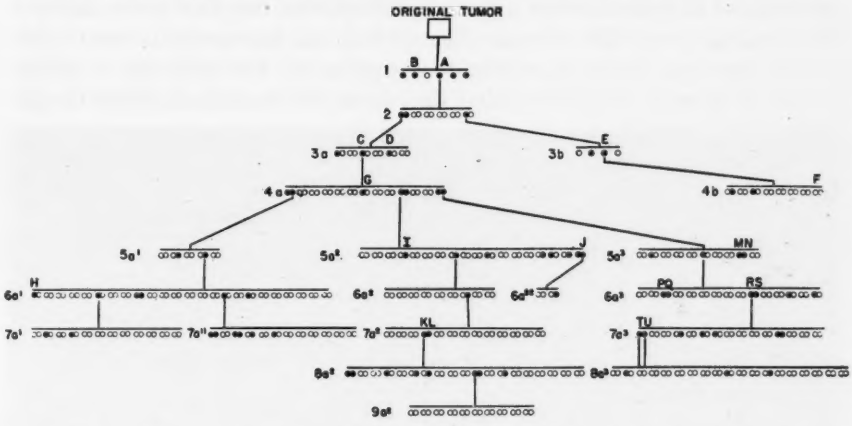

FIG. 9. A family tree representing the serial transplantation of an anaplastic carcinoma of the thyroid from man. The lines reveal the origin of each series of transplantations. A single circle indicates that only one eye of an animal was used for transplantation, two circles indicate that both eyes were simultaneously used. Shaded circles represent those transplants which survived and grew. Circles containing an X show those transplants which survived at least 90 days without gross evidence of growth. Many of the transplants which grew remained dormant for more than 90 days before growth began. Alphabetic notations indicate specific transplants which were studied histologically. (Courtesy of *Cancer*. Dobyns and Lennon (8).)

so that the transplant would have the sole opportunity to pick up the radioactive iodine. No evidence of function was demonstrated in these transplants two days after total thyroidectomy of the host. This does not

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FIG. 7. Follicular adenocarcinoma with the formation of colloid. (Courtesy of *Ann. Surg.* Dobyns and Lennon (7).)

A. A so-called "benign metastasizing struma" removed from a metastasis in the humerus.

B. A histologic section prepared from a transplant which remained in the eye for 272 days.

FIG. 8. Solid cellular carcinoma with very rare acini. (Courtesy of *Ann. Surg.* Dobyns and Lennon (7).)

A. The primary tumor. It was only after considerable search that a microscopic field could be found which had more than one follicle present.

B. Viable tumor removed from the eye 96 days after transplantation. Note that the histologic picture was more differentiated in the transplant than in the primary tumor.

exclude the possibility that function would not have developed if the thyroid of the host had been absent for a long period of time.

One of the very anaplastic carcinomas which grew in 2 of the original 6 transplantations was retransplanted in new experiments through nine generations of animals over a period of three and one-half years, using a total of 430 eyes in 220 animals. The growth and retransplantation of this tumor from one series of animals to another is illustrated by a family tree in Figure 9. It will be noted that from 430 transplantations of this

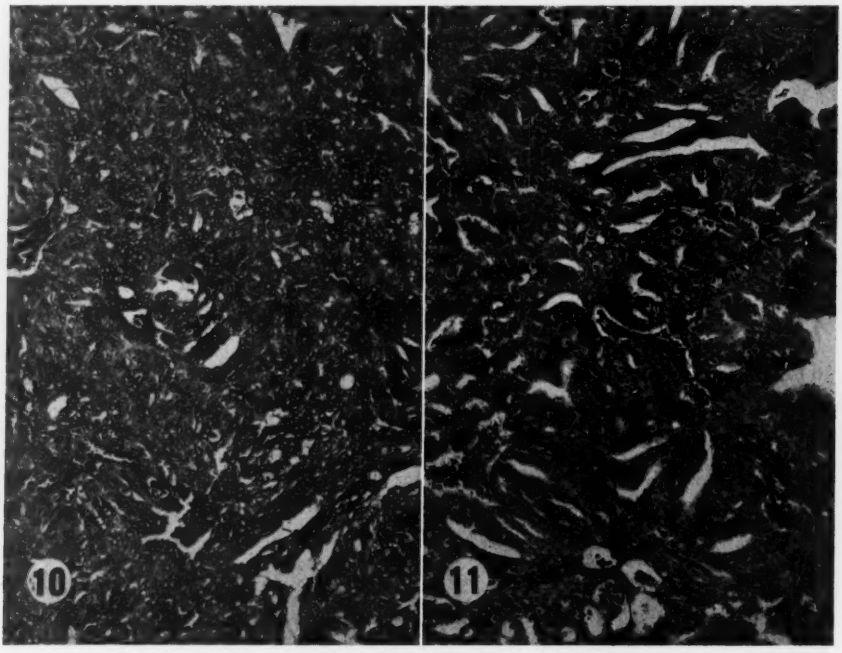

FIG. 10 FIG. 11

FIG. 10. The original tumor removed from a man of 56 years of age. Numerous histologic preparations failed to reveal any evidence of differentiation in this tumor.

FIG. 11. Transplant B in Fig. 9; solid cords of cells and rare poorly formed acini.

(Both figures, courtesy *Ann. Surg.* Dobyns and Lennon (7).)

tumor, 55 growths occurred. The fact that 22 of these growths occurred bilaterally raises interesting speculation concerning the differences in the growth-promoting factors of these animals.

The original tumor (Fig. 10), when removed from the patient, consisted of solid masses of pleomorphic cells. There was considerable evidence of mitotic cellular division. The nuclei were variable in size and contained prominent nuclei and coarse aggregations of chromatin. Abundant micro-

scopic preparations revealed a uniformly undifferentiated histologic pattern throughout.

As retransplantations were made and generations passed, samples of the growing transplants were studied microscopically. A variety of histologic patterns were found to have developed. In general there was a tendency toward more and more differentiation. In some transplants solid cords of cells (Fig. 11) (B in Fig. 9) were found, resembling the structure described by Wegelin (6) as struma nodosa trabecularis. Typical papillary

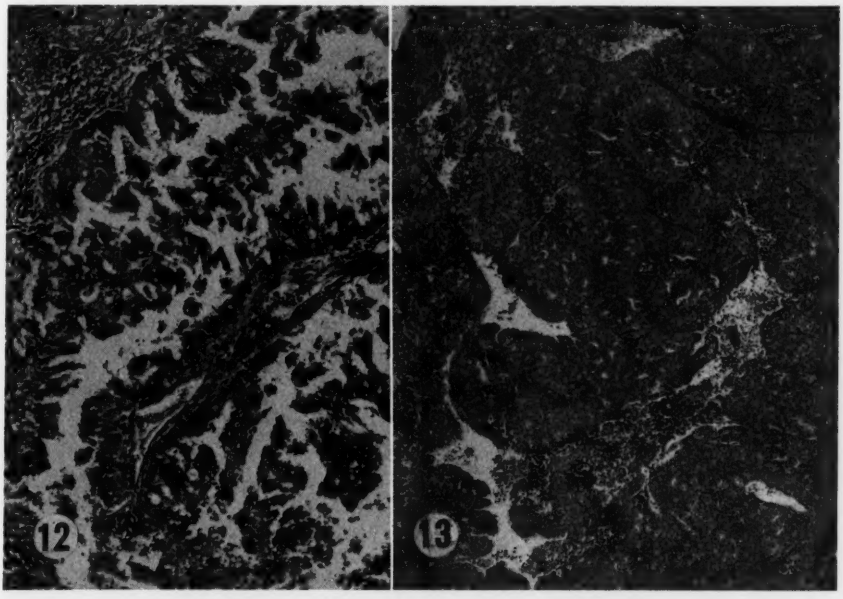

FIG. 12 FIG. 13

FIG. 12. Transplant G in Fig. 9; papillary adenocarcinoma.

FIG. 13. Transplant J in Fig. 9; a histologic pattern consisting of small lobules and cords 50 to 100 cells in width.

(Both figures, courtesy *Cancer*. Dobyns and Lennon (8).)

adenocarcinoma (Fig. 12) (G in Fig. 9) was encountered in the fourth generation. In one branch of the family tree (in series A^2) an unusual histologic pattern (Fig. 13) (J in Fig. 9) was discovered. Two generations later a pattern (Fig. 14) (K in Fig. 9) was found which is not encountered in pathologic human thyroids. A sister transplant of the latter represented another new pattern (Fig. 15) (L in Fig. 9) which was composed of spindle cells forming whirls. These whirls or nests of cells were surrounded by a matrix of large epithelial cells comparable to those seen in the original tumor. Primitive acini composed of 8 to 15 cells occasionally were found

among the early generations of this tumor (Fig. 16); however, in later generations of series A^3 acini were found to be composed of 40 or 50 cells, and these acini contained colloid which was vacuolated at the periphery (Fig. 17). This histologic pattern strongly suggests that a functional capacity may have been present, but unfortunately the host was not given radioactive iodine before this transplant was removed from the eye.

It is not clear what biologic forces caused this undifferentiated tumor to differentiate. Although the patient from whom this tumor was obtained

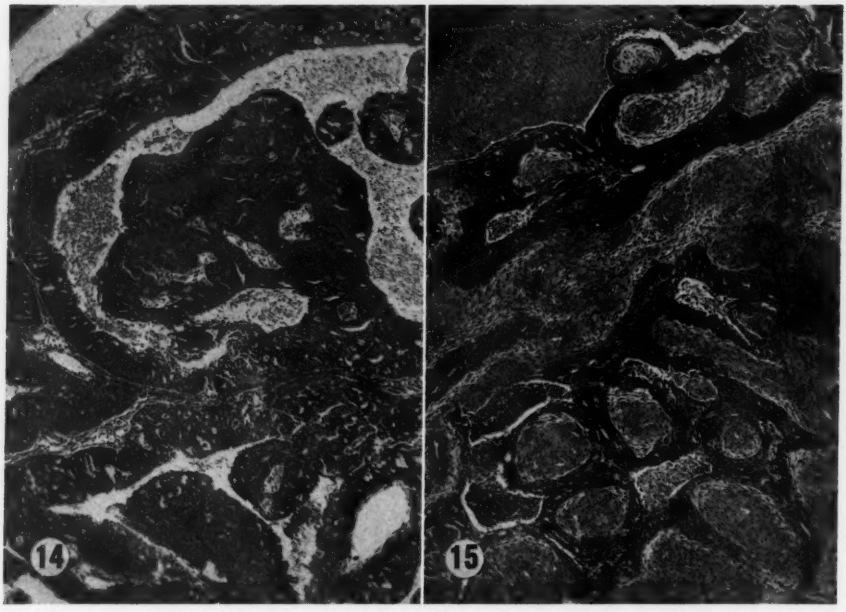

FIG. 14 FIG. 15

FIG. 14. Transplant K in Fig. 9; similar to Fig. 13, but here hollow spheres containing polypoid masses of cells were found.

FIG. 15. Transplant L in Fig. 9; some of this transplant resembled that in Fig. 14 but, as illustrated here, nests of spindle-shaped cells were also found.

(Both figures, courtesy *Cancer*. Dobyns and Lennon (8).)

survived only a few months, the tumor survived three and one-half years in animals. Perhaps if the tumor had had an opportunity to survive for a long time in the patient, it might have become differentiated as it did in the animals.

The changing histologic pattern of this tumor during serial transplantation raises the question of the reliability of classifications of thyroidal tumors. These changing qualities toward differentiation lend support to

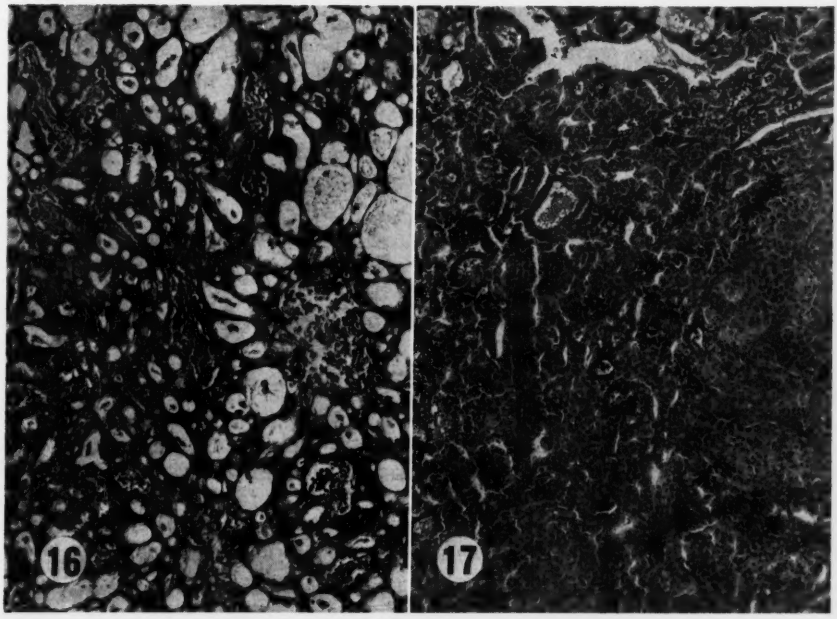

FIG. 16 FIG. 17

FIG. 16. Transplant B in Fig. 9; poorly formed acini were found in a transplant from an early generation.

FIG. 17. Transplant U in Fig. 9; well formed follicles containing colloid were found in a transplant from a later generation.

(Both figures, courtesy of *Cancer*. Dobyns and Lennon (8).)

the effort that is currently being made to induce nonfunctioning carcinomas of the thyroid to acquire function and take up therapeutic quantities of radioactive iodine.

SUMMARY

A variety of human thyroidal tumors have been transplanted into the anterior chamber of the guinea pig's eye. Numerous malignant lesions have survived and grown. Human thyroidal tissue, serving as controls, and benign lesions have had a tendency to be absorbed after relatively short intervals of time; however, the normal thyroidal tissue has been found to survive for as long as ninety days in intact animals. Two primitive fetal adenomas were classified as benign on the basis of morphologic criteria; however, their behavior after transplantation suggested that a diagnosis of malignancy should have been made. The usefulness of the method as a means of distinguishing between benign and malignant lesions of the thyroid requires further investigation.

Following the transplantation of malignant lesions, a tendency towards differentiation has occurred. One very anaplastic tumor has been retransplanted through nine generations in a large number of animals, during which time many different histologic patterns of carcinoma of the thyroid have evolved.

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THE USE OF THYROTROPIC HORMONE (TSH) IN THE DIAGNOSIS OF MYXEDEMA*†

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UNTIL recently, the diagnosis of pituitary myxedema has depended upon the association of hypothyroidism with adrenocortical insufficiency and very low or absent urinary follicle-stimulating hormone (FSH) levels (1). However, the observation that proven primary thyroid myxedema may be accompanied by evidence of adrenocortical insufficiency (2, 3, 4, 5) and low or absent urinary FSH (3) has shed doubt upon the validity of this concept. In certain instances, the differential diagnosis between primary thyroid and pituitary myxedema may be extremely difficult. With the availability of relatively pure thyroid-stimulating hormone (TSH), a technique may now be employed which specifically tests the ability of thyroid tissue to respond to pituitary stimulation. This test is based upon two premises: first, that primary myxedema is due to failure of the thyroid gland, the tissue of which cannot be stimulated to function normally; second, that pituitary myxedema is due to a failure of the pituitary gland to stimulate the thyroid gland, which is, however, potentially capable of being stimulated.

Schrire (6) administered thyrotropin (TSH) to 4 patients with myxedema and in 3 demonstrated increases in pulse rate, basal metabolic rate, urinary creatine excretion and thyroid size. The fourth showed no response and was presumed to be a case of primary thyroid myxedema. Werner and his associates (7) and Querido and Stanbury (8) found that patients with hypopituitarism showed a marked increase in I^{131} uptake after thyrotropin. Werner's group demonstrated, in addition, that serum protein-bound iodine also tends to increase after TSH in pituitary myxedema, but not in primary thyroid myxedema.

Received for publication June 8, 1951.

* Read by title at the Annual Meeting of the Association for the Study of Internal Secretions, Atlantic City, N. J., June 7–9, 1951.

† This study was made possible by a grant from Ciba Pharmaceutical Products, Inc. to the Endocrine Clinics of the Philadelphia General Hospital. The TSH was supplied by Drs. Mote and Cluxton of Armour Laboratories, Chicago.

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TABLE 1. THE EFFECT OF TSH ON THE I^{131} TRACER UPTAKE IN EUTHYROIDISM AND IN HYPOTHYROIDISM OF KNOWN ETIOLOGY

Patient	Clinical diagnosis	1	2	3	4	5
				% I^{131} uptake*		
		BMR, %	Serum cholesterol, mg. %	without TSH	with TSH	diff.
	Euthyroidism					
H.V.		− 6	250	22	52	30
B.M.		− 6	274	29	45	16
D.M.		− 9	185	26	41	15
A.F.		−17	270	23	39	16
M.N.		− 6	523†	18	45	27
	average	*− 9*	*245*	*23.6*	*44.4*	*20.8*
	Primary Thyroid Myxedema					
G.H.	spontaneous	−37‡	770	5	4	−1
J.C.	"	−44	495	7	5	−2
H.M.	"	−40	356	10	2	−8
L.Z.	"	−18‡	304	1	4	3
R.M.	"	−25	463	5	3	−2
M.S.	"		300	7	12	5
A.M.	"	− 2‡	276	7	11	4
A.S.	"	−10‡	322	5	5	0
E.Ru.	"		524	6	5	−1
E.Re.	"	−32	250	7	8	1
J.M.	cretin	−14	290	8	13	5
M.K.	"		224	6	6	0
C.W.	post-thyroidectomy	− 6‡	329	3	12	9
F.G.	"	−14	359	9	16	7
	average	*−28*	*371*	*6.1*	*7.6*	*1.5*
	Hypopituitary Myxedema					
J.Z.	acromegaly (inactive)	−47	228	17	57	40
T.D.	chromophobic adenoma	− 4	311	8	40	32
V.Z.	" "	−20	291	15	54	39
E.S.	" "	−29	385	16	36	20
S.C.	" "	− 5	376	10	40	30
	average	*−21*	*318*	*13.2*	*45.4*	*32.2*
W.M.	chromophobic adenoma		250	20	29§	9
T.M.	Sheehan's syndrome (autopsy)	−28	296	16		
	Total averages hypopituitary group	*−22*	*305*	*14.6*		

We should like to add our experience with TSH in a consecutive series of patients with myxedema, in order to help in the evaluation of this diagnostic method.

MATERIALS AND METHODS

A. The thyrotropic hormone used in this study was a purified lyophilized powder. Vials contained the equivalent of 20, 25, or 30 mg. of the standard Armour TSH powder, and the contents of one vial were dissolved in 2 ml. of sterile saline immediately prior to intramuscular injection.

B. The radioiodine tracer technique was that of Lasche *et al.* (9), excepting that 50 instead of 100 microcuries of I^{131} were administered to the patient and the percentage of the administered dose still remaining in the thyroid twenty-four hours later was determined with a Geiger counter. In this clinic, the following general interpretation is given to the test:

Uptake	*Interpretation*
0– 10%	hypothyroid
11– 15%	equivocal
16– 35%	normal
36– 40%	equivocal
41–100%	hyperthyroid

C. Two to four weeks after the performance of the baseline I^{131} test, three consecutive daily intramuscular injections of from 20 to 30 mg. of TSH were administered. A second tracer dose of I^{131} was given on the fourth day, and the uptake measured twenty-four hours later.

D. Serum cholesterol values between 150 and 300 mg. per 100 ml. were regarded as normal, depending somewhat upon the age of the patient.

E. Basal metabolic rates were regarded as normal when they ranged between plus and minus 15 per cent.

RESULTS

A. *Normal individuals.* Baseline I^{131} values were, as expected, within the normal range. After TSH administration, there was a marked increase

Footnotes to Table 1

* Column 3: baseline tracer before TSH.
Column 4: tracer following TSH.
Column 5: difference between values in columns 4 and 5.

† Idiopathic hypercholesterolemia; value not included in average.

‡ BMR unreliable because of mental or cardiac status, or poor tracing; not included in average.

§ This patient was taking cortisone during the administration of TSH; not included in average of first group.

in radioiodine uptake by the thyroid gland, often up to hyperthyroid levels. Several control patients showed mild elevations of temperature, slight increases in pulse rate, and enlargement and occasionally tenderness of the thyroid gland. Mild and localized pain was often produced at the injection site. The radioiodine tracer values, together with the other pertinent laboratory data, are shown in Table 1.

B. *Primary thyroid myxedema.* All patients had clearcut cases of primary thyroid myxedema, spontaneous or postoperative. They demonstrated thick dry yellow skin, sparse coarse scalp hair, slow pulse and symptoms of severe hypometabolism. Diagnosis was made without reference to the TSH test. Baseline uptakes of I^{131} tracers fell between 1 and 10 per cent (Table 1). After TSH, no significant change was noted, the I^{131} tracer uptakes remaining between 2 and 16 per cent. The greatest increase in I^{131} pickup was noted in Patients C. W. and F. G., in whom myxedema developed postoperatively, suggesting the presence of a remnant of responsive thyroid tissue.

C. *Pituitary myxedema.* Cases in this group showed unequivocal clinical and laboratory evidence of panhypopituitarism. The pituitary lesions were diagnosed by means of x-ray examination of the skull and by visual field determinations, supplemented in one case by operation and biopsy, and in another by autopsy. The baseline I^{131} tracer uptakes (Table 1) ranged from 8 to 20 per cent, somewhat higher than those of the primary thyroid group. With the exception of 1 patient (W. M.) who was receiving 25 mg. of oral cortisone a day during the period of thyrotropic stimulation, these patients showed a marked increase in radioiodine uptake following TSH administration, similar to that noted in normal individuals.

D. *Myxedema of uncertain etiology.* This group included patients in whom the primary etiology could not be definitely determined by the usual clinical means. As will be seen in Table 2, there were 2 patients (M. R. and V. H.) in whom the disease was thought to be of pituitary origin, who did not respond to TSH stimulation; and 1 patient (W. B.), considered to have primary thyroid myxedema, whose thyroid uptake of I^{131} was greatly increased after TSH administration. The I^{131} uptake of the remaining patients after TSH was in accordance with the original clinical impression. We are inclined to change our clinical diagnosis to conform with the TSH findings, in view of the definite differences noted in patients with myxedema of certain etiology.

E. *Reproducibility of TSH test and effect of thyroid medication.* Two patients with pituitary myxedema were given 1 grain of desiccated thyroid daily for three months and the TSH test repeated (Fig. 1). No significant differences between the first and the second tests were observed,

TABLE 2. THE USE OF TSH TO DETERMINE THE ETIOLOGY OF THE HYPOTHYROID STATE

Patient	Clinical impression	1	2	3	4	5
				% I^{131} uptake*		
		BMR, %	Serum cholesterol, mg. %	without TSH	with TSH	Final diagnosis
M.R.	Sheehan's syndrome	−40	616	5	5	Primary thyroid myxedema
V.H.	Hypopituitarism	−24	149	4	4	Cretinism
E.A.†	Sheehan's syndrome	−15	360	9	57	Sheehan's syndrome
B.P.†	" "		260	5	35	" "
E.C.	Hypopituitarism	−18	311	14	36	Hypopituitarism
H.J.	"		323	15	59	"
A.A.	"	−27	295	10	47	"
W.B.	Primary thyroid myxedema	−25	488	13	42	"

* Column 3: baseline tracer before TSH.
Column 4: tracer following TSH.

† E.A. and B.P. were studied at Temple University Hospital, the latter through the courtesy of Dr. Harold Hyman.

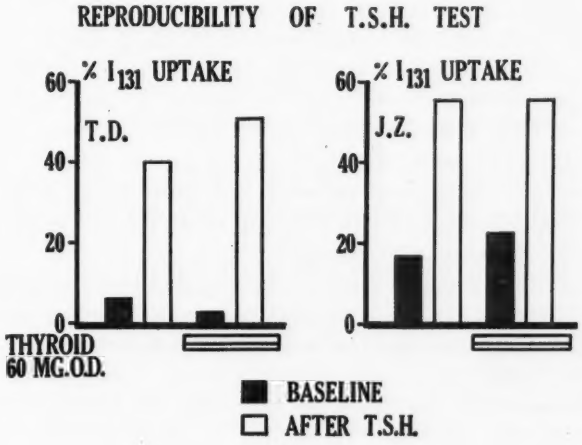

FIGURE 1

demonstrating not only the reproducibility of the results, but also indicating that this dose of thyroid does not prevent the thyroid-stimulating effect of exogenously administered thyrotropin. It also suggests that the first course of thyrotropic hormone did not elicit enough antihormones or antibodies to interfere with the second test.

DISCUSSION

Although integrity of the anterior pituitary gland is essential for the maintenance of normal thyroid function, it appears from our data either that the thyroid has the inherent capacity to metabolize iodine even though at a reduced rate in the absence of pituitary stimulation, or that in hypopituitarism the pituitary still has some residual thyroid-stimulating activity. The average uptake of radioactive iodine by the thyroid gland in patients with thyroid myxedema was 6.1 per cent (in no instance over 10 per cent), whereas in pituitary myxedema it was 14.6 per cent, only one uptake being below 10 per cent. Most of the values in the latter group were within the low-normal range. The mean BMR of −28 per cent and serum cholesterol of 371 mg. per cent in the thyroid myxedema group, when compared to values of −22 per cent and 305 mg. per cent, respectively, in the hypopituitary group, would appear to confirm this possibility.

The change in the mean thyroid radioiodine uptake after TSH is also informative. As one might anticipate on theoretical grounds, there was no significant change in the patients with primary thyroid myxedema. Patients with pituitary myxedema, however, showed a greater increment of iodine pickup after TSH than did normal subjects but only because of the lower baseline levels. The mean pickup of the normal group before TSH was 23. 6 per cent compared to 13.2 per cent for the patients with pituitary myxedema. After thyroid stimulation, these values were 44.4 and 45.4 per cent, respectively, almost identical figures. It may be that, with a given dose of TSH, a limited response of thyroid function is possible, regardless of the prior state of pituitary stimulation. Under these circumstances, the thyroid glands of patients with normal and with insufficient pituitaries might be expected to react up to a certain maximum level to an exogenously administered stimulus.

It is theoretically possible that the thyroid glands of patients with long-standing pituitary myxedema may finally become unresponsive to limited doses of TSH. Querido and Stanbury (8) have reported such a case. We question the frequency of such unreactiveness since certain of our patients, J. Z. and S. C., had had the syndrome for five and twenty-eight years, respectively, and still responded to TSH stimulation. Further study is required to clarify this point.

It is apparent (Fig. 1) that similar results may be anticipated when the TSH test is repeated in the same patient. It would also seem that 1 grain of desiccated thyroid daily is insufficient to change the test appreciably. Larger doses of thyroid should be used in order to determine the possible effect on the action of TSH. It is interesting to note in this connection that Stanley and Astwood (10) obtained increases in the accumulation gradient of radioiodine with TSH, in patients who were taking several grains of thyroid a day.

Although the primary etiology of myxedema is generally obvious, there are many patients in whom the diagnosis cannot be made with certainty. The ability of TSH to stimulate the radioiodine uptake of the receptive thyroid gland may be of aid in this group.

SUMMARY AND CONCLUSIONS

1. In this series, patients with pituitary myxedema appeared to have a more nearly normal level of thyroid function than did those with thyroid myxedema, as evidenced by the higher I^{131} uptakes and BMR's and the lower serum cholesterol values.

2. Thyrotropic hormone (TSH) administration in conjunction with a 24-hour radioiodine tracer test has proven to be an accurate method of distinguishing known cases of pituitary myxedema from primary thyroid myxedema. Euthyroid individuals showed a mean increase of 20.8 per cent over baseline values. Primary hypothyroid patients maintained a radioiodine accumulation (7.6 per cent) similar to their low control values (6.1 per cent). Pituitary hypothyroid patients showed a mean increase of 32.2 per cent, their mean post-stimulation value (45.4 per cent) being almost identical with that of the euthyroid group (44.4 per cent).

3. The TSH test was reproducible in 2 patients with pituitary myxedema; 1 grain of desiccated thyroid daily did not alter the results.

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RADIOIODINE TRACER STUDIES IN THIOCYANATE MYXEDEMA*

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ALTERATIONS in the function of the thyroid gland associated with the administration of potassium thiocyanate have been recognized clinically for a number of years. In 1936 Barker (1) observed 3 patients in whom during treatment with potassium thiocyanate "peculiar myxedematous swelling of the tissues of the face, orbital areas, and cervical region" developed. Thyroid enlargement was noted in 2 of them. Basal metabolic rates varied from −9 to −18 per cent. Later, Barker and associates (2) reported that in 9 of 246 patients so treated, large thyroids and myxedematous facies developed. Their metabolic rates were "in the neighborhood of −10." Both goiter and myxedematous symptoms disappeared when desiccated thyroid was given. Similar observations have been reported by others (3, 4, 5). Estes and Keith (6) reported a case in which there were myxedematous symptoms without enlargement of the thyroid during thiocyanate therapy. Omission of thiocyanate was followed by prompt disappearance of myxedematous symptoms without replacement therapy with thyroid.

In 1943 Rawson, Hertz and Means (7) reported detailed studies of 2 cases of thiocyanate goiter with myxedema. Biopsy of the thyroid in 1 case disclosed extreme hyperplasia with marked papillary overgrowth similar to that seen in severe exophthalmic goiter. Similar histopathologic changes were noted by Potter in 2 cases (8). In 1 of their cases Rawson and associates observed increased thyroidal uptake of I^{131}. Experimentally, Rawson, Tannheimer and Peacock (9) observed increased accumulation of radioiodine in rats' thyroid glands which had previously been made hyperplastic by the administration of thiocyanate.

Subsequent work by Astwood (10) and VanderLaan and Bissell (11) indicated that the thyroid of the rat retained the property of specifically concentrating inorganic iodide, even when hormonal biosynthesis was

Received for publication July 23, 1951.

* Read at the Annual Meeting of the American Goiter Association, Columbus, Ohio, May 24, 1951.

This article will be included in the bound volume of the "Transactions of the American Goiter Association" published by Charles C Thomas, Publisher, which will be available for sale early in 1952.

TABLE 1. DATA ON PATIENTS IN WHOM MYXEDEMATOUS SYMPTOMS OR THYROID ENLARGEMENT DEVELOPED DURING TREATMENT WITH POTASSIUM THIOCYANATE

Case	Sex	Data on Admission								Maximal change after discontinuing potassium thiocyanate therapy								
		Thyroid size*	Basal metabolic rate, per cent	Serum protein-bound iodine, micrograms per 100 cc.	Cholesterol, mg. per 100 cc.	I^{131} in urine at 48 hours, per cent of dose	I^{131} extra-renal disposal rate, per cent per hour	I^{131} 24-hour *in vivo* count, per cent of dose	Serum potassium thiocyanate level, mg. per 100 cc.	Interval, weeks	Thyroid size*	Basal metabolic rate, per cent	Serum protein-bound iodine, micrograms per 100 cc.	Cholesterol, mg. per 100 cc.	I^{131} in urine at 48 hours, per cent of dose	I^{131} extra-renal disposal rate, per cent per hour	I^{131} 24-hour *in vivo* count, per cent of dose	Serum potassium thiocyanate level, mg. per 100 cc.
1	M	iii	+5		234	70.4	1.1		7.9									
2	F	i	−23			71.9	1.4	8.8	11.8									
3	M	ii	−23	0.5	260	80.4	0.8	2.5		25	0	−6	6.4					
4	F	ii	−21	1.1	343	78.7	1.0	10.1	6.8	8	i	+2	4.0	240	21.2	22.2	74	0.1
5	M	iii	−6	0.6	210	63.3	1.07	17.2	11.6	11	i	+8	5.4		23.2	14.4	52.3	0.7
6	F	i	−8		373	55.9	2.8	25.0	6.9	3	i	+8		187	41.0	6.2	58	1.5
7	F	iv	−3		230	94.2	0.05	4.54	11.4	8	i	−5			8.2	46.7		
8	F	ii	−17		234	65.3	1.6	21.0	4.7	2	i	−3		267	34.5	8.8	39.4	1.9
9	F	iv	+6		353	45.0	2.4		6.5	8	0	+20		230	23.7	16.8		0.3
10	F	i	−14	0.4	283	70.0	1.2	6.9	10.8	7	i	+5	4.0		25.9	7.7	48.0	1.2
11	F	i	−18	0.3	343	69.3	1.1	13.3	11.3	3	i	−3	2.2	230	33.4	17.5	69.7	2.2
12	F	iv	−12	0.4	317	60.0	1.59	8.7	6.3	2	ii	−12	1.6	254	26.6	9.49	58.5	1.3
13	M	ii	−24	0.2	340	70.8	0.7	4.4	17.1	4	i		4.0		28.5	8.01	43.9	2.4
14	F	ii	+3		184	32.4	13.25	43.0	6.0	1	i			203	34.4	11.4		2.5
15	F	0	−15		305	88.2	0.3	1.26	13.0	16	0	−28		327	61.4	1.2	1.97	0.2
16	M	ii	+6		190	84.1	0.9	4.0	11.9	4	i	+3		184	44.1	14.8	39.1	0.4
17	F	ii	+21		137				6.9	1	ii	+7	3.0		27.2	20.7	65.9	0.3

* Thyroid size; 0 = not palpable; i = less than 25 Gm.; ii = 25–50 Gm.; iii = 50–100 Gm.; iv = more than 100 Gm.

halted by thiouracil. Franklin, Chaikoff and Lerner (12) and VanderLaan and VanderLaan (13) found that this specific iodine-trapping function was poisoned or abolished by thiocyanate.

In view of these experimental studies, it seemed desirable to obtain more detailed clinical observations on the behavior of thiocyanate goiter in man.

METHODS AND MATERIALS

Fifteen patients were observed in whom myxedematous symptoms developed during treatment with potassium thiocyanate for hypertension. There were 4 men and 11 women. Ages ranged from 48 to 64 years. In 2 additional patients thyroid enlargement without clinical evidence of hypothyroidism was found to occur. Basal metabolic rates, serum protein-bound iodine, level of plasma cholesterol, and radioiodine tracer studies were obtained and, when possible, repeated at intervals. Serum protein-bound iodine was determined by the method of Barker (14). Radioiodine tracers of 100 microcuries of I^{131} were given orally with 100 micrograms of sodium iodide as a carrier. Urinary and thyroidal observations were made by the method of Keating and associates (15).

OBSERVATIONS

The initial data for all 17 cases are summarized in Table 1. Basal metabolic rates were not as low as one would expect with comparable degrees of spontaneous myxedema. Levels of plasma cholesterol were usually elevated. Serum protein-bound iodine was within the range characteristic of myxedema.

Radioiodine tracer studies were made in all cases. In all but 4 instances (Table 1, Cases 5, 6, 9 and 14) the amount of iodine excreted in the urine in forty-eight hours was greater than normal.[1] The extrarenal disposal rate[2] (15), which provides an indirect measure of the rate of radioiodine accumulation by the thyroid, was low in all instances save 1 (Table 1, Case 14). *In vivo* measurements were made over the thyroid gland twenty-four hours after administration of the dose in 13 cases. These measurements were less than normal[3] in 11 instances.

The impaired ability of the thyroid to collect radioiodine could not be correlated with the duration of thiocyanate therapy, size of the gland, or duration of myxedematous symptoms. However, a rough correlation did exist between concentration of thiocyanate in the blood and accumulation of radioiodine by the thyroid (Fig. 1). The highest thiocyanate

[1] Mean value for 157 normals = 63.5 ± 0.8 per cent (16).

[2] Mean value for 157 normals = 3.9 ± 0.1 per cent per hour (16).

[3] Mean value for 98 normals = 24.7 ± 1.2 per cent (16).

* Thyroid size; 0 = not palpable; i = less than 25 Gm.; ii = 25–50 Gm.; iii = 50–100 Gm.; iv = more than 100 Gm.

concentrations in the blood accompanied the lowest radioiodine collections. As the concentrations of thiocyanate in the blood fell after withdrawal of the drug, the thyroid regained its ability to collect labeled iodine.

The interval between commencing treatment with potassium thiocya-

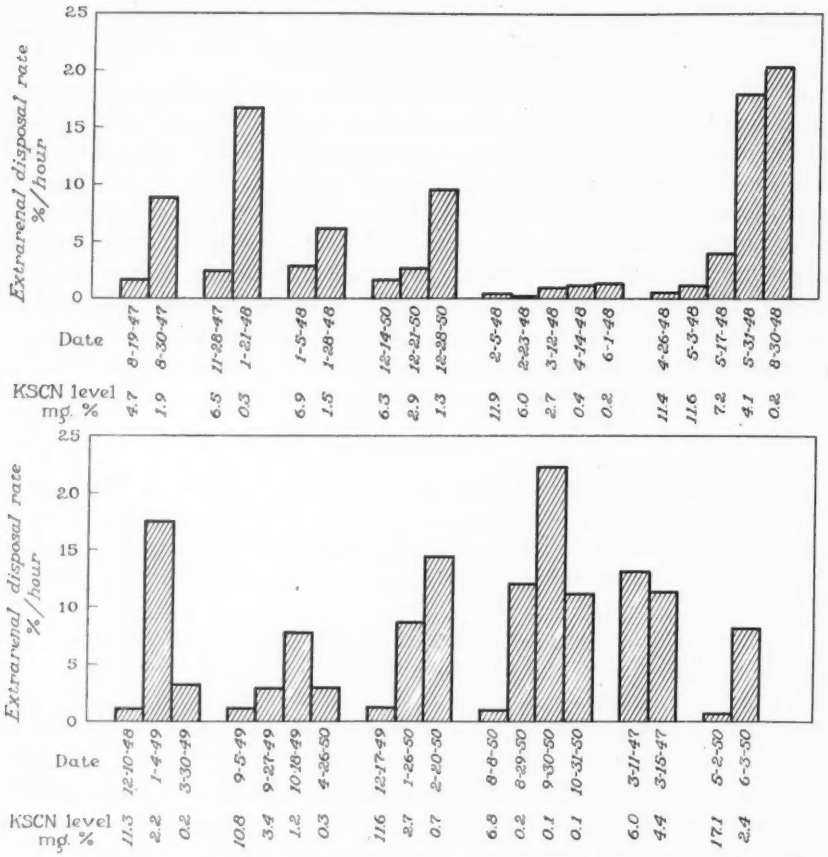

FIG. 1. Extrarenal disposal rates (a measure of thyroidal accumulation of radioiodine) obtained at intervals after omission of thiocyanate. In all except 1 case serial tracer studies showed increased rates of accumulation of radioiodine by the thyroid as blood levels of thiocyanate fell.

nate and the subsequent development of signs of thyroid deficiency was variable, ranging from six to sixty months and averaging thirty-one months.

Duration of treatment with thiocyanate could not be correlated with

intensity of clinical myxedema, the size of the thyroid gland, or even the presence or absence of a goiter. In 1 case (Table 1, Case 15) no thyroid tissue was palpable. Ten of the patients (67 per cent) showed thyroid enlargement varying from barely detectable goiter to massive diffuse enlargement of both lobes. Four patients had normal or minimally enlarged thyroid glands, though 1 of these had been taking thiocyanate for ten years. The most pronounced thyroid enlargement was encountered in 3 patients none of whom had been taking the drug for longer than eighteen months.

Thyroidectomy was performed in 2 cases. The first patient (Table 1, Case 1) had been known to have a nodular goiter prior to the development of thiocyanate myxedema. Thyroidectomy was performed two weeks after thiocyanate treatment had been stopped. The histopathologic character of the gland was that seen in the usual multiple adenomatous goiter, though a few areas of extra-adenomatous hyperplasia were noted. The second patient (Table 1, Case 10) underwent subtotal thyroidectomy because of persistent nodularity of the thyroid, eight months after the organ had undergone its maximal degree of spontaneous involution following withdrawal of thiocyanate. The histopathologic character was similar to that seen in the first case, though no areas of hyperplasia were seen.

Table 1 contrasts the initial laboratory data with similar data collected from the same patients after withdrawal of potassium thiocyanate. Omission of the drug was usually followed by a characteristic series of events. The myxedematous symptoms began to abate promptly in most cases, noticeable change usually occurring within seven to fourteen days. The goiter, if present, became smaller at the same time.

As the level of thiocyanate in the blood fell, the initial low uptake of radioiodine was replaced by an avidity for iodine which usually reached a degree seen only in the diffuse hyperplastic thyroid of exophthalmic goiter. These changes are illustrated for one case in Figure 2. This hyperfunctioning phase persisted for many weeks. In the 4 cases followed the longest, radioiodine collection either returned to normal or had begun to do so two and a half to six months after treatment with thiocyanate was discontinued. In 2 cases (Table 1, Cases 5 and 9) an increased avidity of the thyroid for iodine was still present when the patients were last studied one and a half and two and a half months, respectively, after therapy had been stopped.

One patient (Table 1, Case 15, Fig. 3), unlike the rest, did not show spontaneous improvement of myxedematous symptoms following omission of potassium thiocyanate. Four months later, although levels of thiocyanate in the blood had been negligible for weeks, the basal metabolic rate remained low and clinical myxedema remained unaltered. Administration

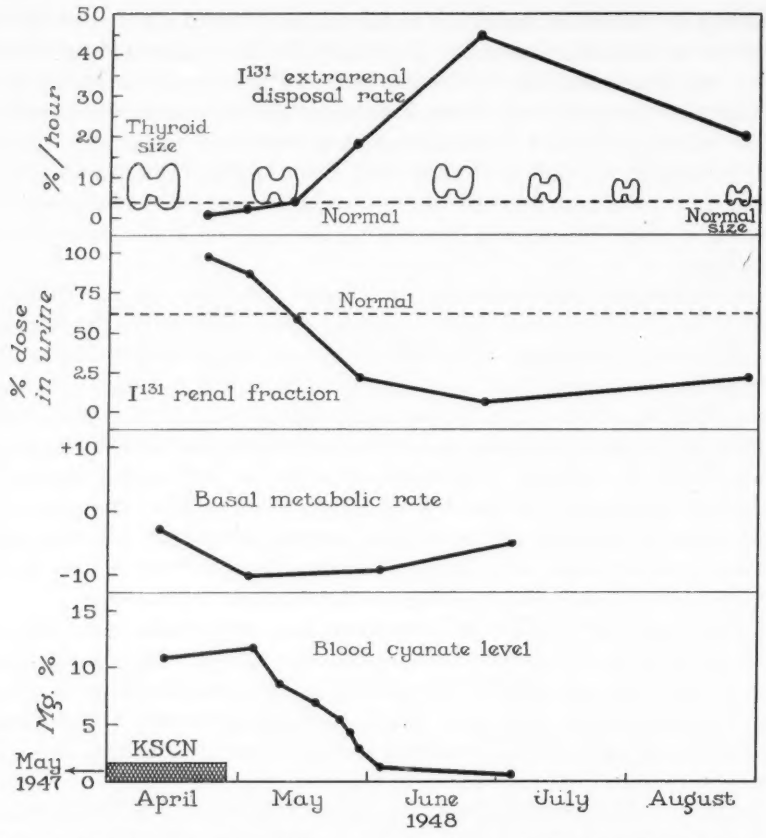

FIG. 2. Alterations of accumulation of radioiodine and other functions in Case 7. The initial suppression of I^{131} uptake was followed by an abnormally high uptake which persisted for months. With 1 exception, all cases studied showed a similar sequence of events following withdrawal of thiocyanate.

of desiccated thyroid at this time promptly restored the patient to a euthyroid condition.

In 2 patients goiters were observed to develop without any clinical symptoms of myxedema (Table 1, Cases 16 and 17). Both patients exhibited moderate diffuse enlargement of the thyroid gland but were otherwise well. Withdrawal of the drug was followed by increased accumulation of labeled iodine by the thyroids and gradual disappearance of the goiters.

COMMENT

In the cases of thiocyanate myxedema presented here, the initial basal metabolic rates tend to be higher than those usually seen in spontaneous

or postoperative myxedema. Whether the familiar tendency for hypertension to elevate the basal metabolic rate is a sufficient explanation for this discrepancy is uncertain.

Case 15 differed from the others by showing no recovery of radioiodine collection or abatement of myxedematous symptoms following discontinu-

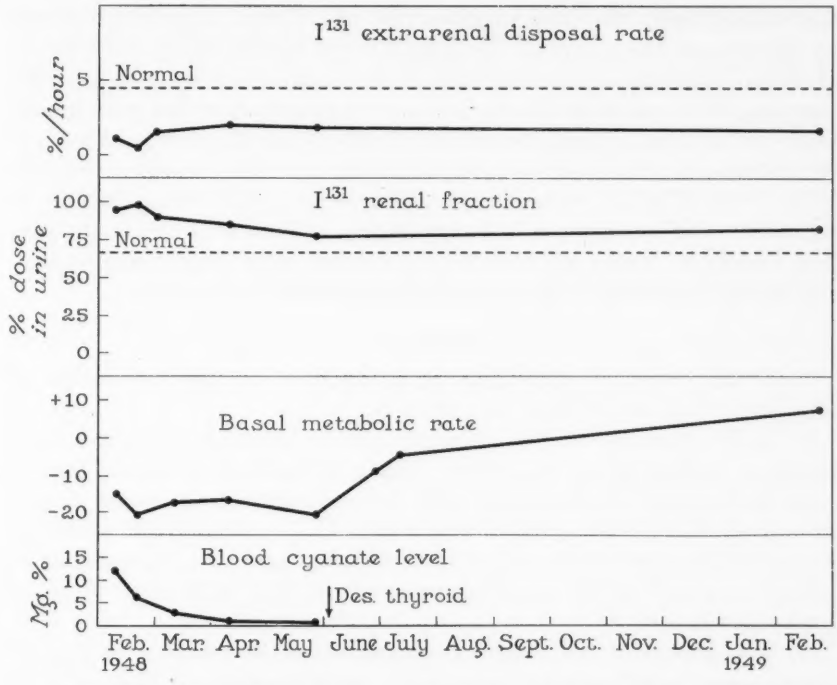

FIG. 3. Lack of change in accumulation of radioiodine in Case 15 as the level of thiocyanate in the blood fell following withdrawal of the drug. The series of events depicted in Figure 2 did not occur in this case. The basal metabolic rate remained low and myxedematous symptoms persisted until desiccated thyroid was given, suggesting that the myxedema was of spontaneous origin and unrelated to the administration of thiocyanate.

ance of thiocyanate therapy. One wonders whether this is spontaneous myxedema occurring in an individual taking potassium thiocyanate or whether the drug produced a permanent depression of thyroid function.

Our observations support those of others in indicating that potassium thiocyanate is sometimes capable of inducing symptoms of myxedema in human subjects, frequently with associated enlargement of the thyroid. The mechanism is presumably the same as in laboratory animals. It is,

however, difficult to fit into the usual hypothetical pattern the 2 cases in which thyroid enlargement occurred without clinically evident thyroid deficiency.

Thyroidal radioiodine accumulation was usually impaired when the level of thiocyanate in the blood was high. Radioiodine accumulation rapidly increased to abnormally elevated values when the thiocyanate concentration subsequently fell. This suggests that the thyroid made hyperplastic by thiocyanate has an avidity for iodine similar to that seen in the thyroid of exophthalmic goiter, and that this avidity manifests itself as soon as the chemical block imposed by the presence of thiocyanate has presumably been removed by falling blood levels. Furthermore, the increased avidity for radioiodine which follows is accompanied by a fairly rapid involution of the thyroid gland toward normal dimensions and a disappearance of myxedematous symptoms. It is interesting to note that the compensatory increased avidity for radioiodine occurred even when palpable thyroid enlargement was not present (Table 1, Cases 6, 10, and 11).

SUMMARY

1. Fifteen cases of myxedema resulting from the administration of potassium thiocyanate have been studied.

2. In 10 instances thyroid enlargement was present, varying from a barely detectable goiter to massive diffuse enlargement of both lobes.

3. In this series of cases high levels of thiocyanate in the blood usually interfered with the accumulation of radioiodine by the thyroid gland, as evidenced by lowered extrarenal disposal rates and twenty-four-hour *in vivo* counts, and by an increased urinary excretion of labeled iodine at forty-eight hours.

4. Withdrawal of potassium thiocyanate usually resulted in prompt spontaneous subsidence of myxedema, disappearance of the goiter if present, and a marked though temporary increase in the ability of the thyroid gland to collect radioiodine.

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CHANGES IN BLOOD IODINE FRACTIONS AND RADIOACTIVITY UNDER THERAPY*†

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SEVERAL reports (1, 2) indicate that thyroid function can be distorted by therapy with I^{131}. In fact, one of the present authors reported with Dr. F. Homburger that both qualitative and quantitative changes in the blood iodine fractions occurred. This tradition has led to a disregard of the orderliness of thyroid physiology, even under conservative therapy. Nevertheless, if preliminary test doses could afford an accurate preview of thyroxine turnover under therapeutic conditions, a more accurate control of therapeutic dosage would be possible. It is the purpose of this communication to demonstrate the orderliness of thyroxine metabolic turnover even under dosage as high as 50 millicuries of radioiodide, I^{131}.

The data concern the function of the thyroid during the first week after a single dose of radioiodide. They do not involve the stage of marked inflammation and autolysis which follows. Within this interval a striking result emerges, namely, that the daily production of radioactive hormone is essentially independent of isotope dosage, but directly dependent upon the status of the patient as measured by the concentration of serum "hormonal" (protein-bound) iodine.

EXPERIMENTAL PLAN

The orderliness of thyroid function under conservative therapy was demonstrated by two means:

First, the pickup of isotope in the gland was measured in relation to

Received for publication Sept. 7, 1951.

* Read at the Annual Meeting of the American Goiter Association, Columbus, Ohio, May 24, 1951.

This article will be included in the bound volume of the "Transactions of the American Goiter Association" published by Charles C Thomas, Publisher, which will be available for sale early in 1952.

† Aided by grants from the Anna Fuller Fund, the Connecticut Cancer Society and the Fluid Research Fund of Yale University School of Medicine.

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circulating iodide and organically bound iodine, in both stable and radioactive forms. These data were amplified by collateral measurements of serum, urine and exhaled air.

Secondly, the rate of production of radioactive thyroxine was estimated from serial analyses of the blood, for comparison with the functional status of the patient.

METHODS

Radioactivity of the thyroid. Measurements of the gland's radioactivity were made by means of a suitably calibrated Tracerlab Laboratory "Monitor," Model No. Su-3A, with which readings could be made directly in counts per minute on any one of three scales. A wide-angle Geiger-Mueller counter was employed. Thus, in patients too sick to be moved to a laboratory equipped with a bigger machine, measurements could easily be recorded at the bedside. Collateral "body" determinations (as opposed to blood and urine samples) were made to gauge the background.

Exhaled air. The radioactivity of the air exhaled by a patient after treatment with I^{131} is fleeting. It must be measured in a steady stream of exhalation, and can be detected both by an ionization meter and with a Geiger-Mueller counter. The value for exhaled radioactivity must be corrected for the background value of the face and mouth. Such measurements are illustrated in Figure 1. In performing the quantitative test, the background radiating from the face was measured while the patient held his breath, and this value was subtracted from the maximal value attained while the patient was forcibly exhaling. Because of the lag in the counting-rate meter, it was necessary to obtain a series of forcible expirations in order to build up the meter reading to a maximal level.

Radioactivity of serum. The radioactivity of the serum was determined in terms of (a) the inorganic (iodide) fraction and (b) the "hormonal" (protein-bound) fraction. The method used for separating these was the cold-acetone precipitation of Salter and Johnston (3), as modified by Salter and Rosenblum (4). The determination of radioactivity in these fractions was made in small stainless-steel dishes (2.5 cm. in diameter), while housed in the lead shield or "pig" identified as Tracerlab No. SC-9C. Counts per minute were determined with an autoscaler (Tracerlab Model No. SC-1B). Alternatively, after small (test) doses, at least 4 ml. of serum was represented in each fraction determined and this amount was placed in dishes measuring 4 cm. in diameter. This larger sample ensured readings well above twice the background reading.

Correction for internal absorption and geometry was made by the "$x:(x+a)$ method" described by Salter, Johnston and Gemmel (5). In this technique the known radioactivity, a, is selected to be as nearly equal to x as possible. Thus, four determinations of radioactivity in counts-per-minute were averaged and calculated.

Physical decay was controlled automatically, because the a sample just mentioned was derived from a monitor aliquot of the original source of radioactivity, set aside at the outset of the observations. In this way the observed data could be expressed as percentages of the dose administered. Therefore, the pertinent observations reflect biologic decay only.

Radioactivity of urine, alkalinized with ammonia, was determined similarly, after suitable dilution.

Determination of I^{127}. Routine chemical determinations of serum iodide and protein-bound iodine were made by the procedure described by Salter and Rosenblum (4). The

urine, after appropriate dilution, was analyzed by this method or by the titrimetric procedure of Groák (6).

Selection of patients. Patients with varying degrees of thyroid function were selected, who had not received any medication with iodine-containing drugs for at least three months. In addition, any who had undergone gall-bladder studies or Lipiodol injection or inhalation within a year, were discarded. To each fasting patient the dose of I^{131} was administered in Eastern sea-coast tap water, without added carrier. At least 250 ml. of water was ingested, and the patient was not allowed food or drink for an hour thereafter.

1. THYROID PICKUP OF I^{131} (CLEARANCE)

The orderly behavior of thyroid function under therapy is illustrated by Figures 1 and 2, combined.

Euthyroidism with hyperplasia. In Figure 1 are shown the findings in Patient SA, Case #N.V. 54651. This white male, aged 30 years, had suf-

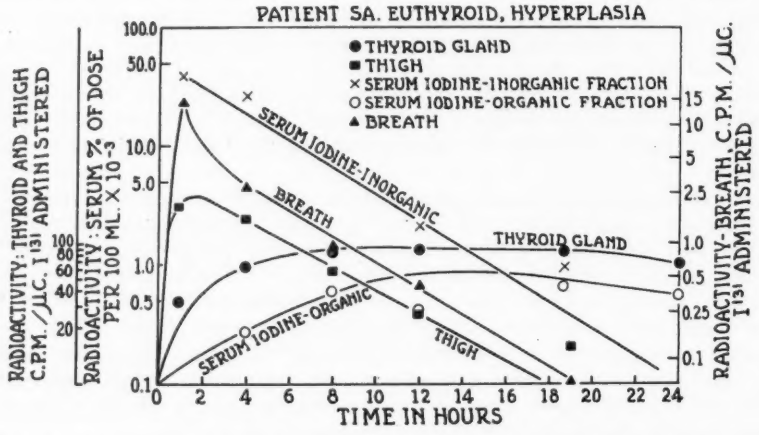

FIG. 1. Measurements of radioactivity at various anatomic sites and in serum. The patient represents Graves' disease in a euthyroid phase, with residual hyperplasia of the gland.

fered from Graves' disease for three years. He was finally seen in a spontaneously euthyroid phase, with residual enlargement of the gland. The serum protein-bound (organic) iodine was 6.2 micrograms per cent. The medication was 5 millicuries of I^{131}. The orderly, semilogarithmic responses shown in the figure are compatible with the "thyroid clearance" for test doses described by Keating and Albert (7) and by Pochin (8). For comparison, studies are given in Figure 2, showing the response to a test dose in hyperthyroidism.

Hyperthyroidism (primary Graves' disease). In Figure 2 are shown the

findings in Patient VA, Case #H.H. 671-501. This white female aged 26 years was obviously thyrotoxic. The serum protein-bound iodine was 12.6 micrograms per cent. The inorganic fraction was 1 microgram per cent. The test dose was only 100 microcuries of I^{131}. Note that as the tracer was trapped rapidly in the gland, the radioactivity of the breath fell sharply, as did the serum iodide (inorganic). The rise in radioactivity of serum

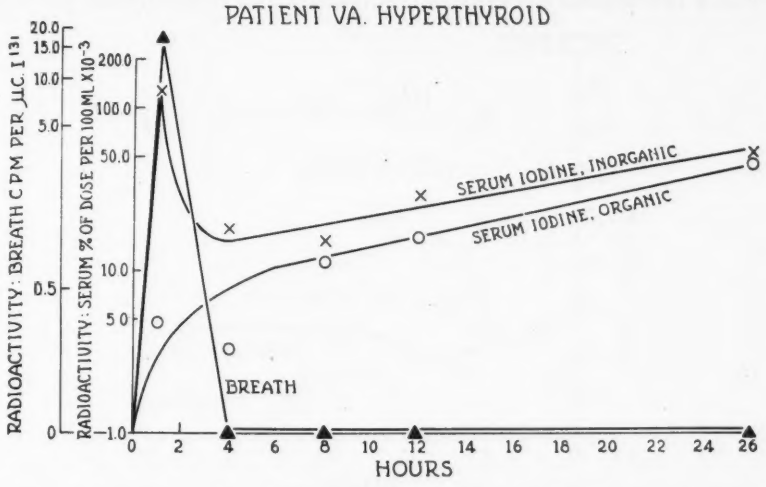

FIG. 2. In hyperthyroidism, the serum labelled *iodide* and the exhaled radioactivity drop sharply as the tracer is fixed in the gland. Later, however, serum iodide rises.

protein-bound iodine (SHI) reflects the high *functional activity* of the gland. The secondary rise in the inorganic fraction (iodide) presumably reflects the rapid peripheral breakdown of recently labelled hormone.

Comment. Our earlier work (1) with patients under treatment with I^{131} indicated that *ultimately* the chemical findings in their blood simulated those of spontaneous hyperthyroidism. The observations on Patient SA (Fig. 1), however, resemble closely our routine findings (not shown) for test studies in euthyroidism. In particular, the steady decline of *inorganic* radioiodine shown in Figure 1 is characteristic of euthyroid patients when they are given a test dose (7, 8). For comparison, Figure 2 shows the response of a spontaneously hyperthyroid patient to a test dose, with the typical secondary rise of the level of radioactivity in the inorganic fraction of the serum, probably due to the rapid rate of breakdown by peripheral tissues of recently labelled hormone.

2. RATE OF PRODUCTION OF RADIOACTIVE THYROXINE

Patients studied. The 21 patients studied (listed in the Appendix) consisted of a) individuals with spontaneous myxedema or individuals made

athyreotic through treatment for thyroid neoplasm; b) euthyroid patients suspected of heart disease or smouldering thyrotoxicosis; c) nontoxic goitrous individuals, either spontaneously so, or after prolonged treatment with propylthiouracil; and d) patients with frank thyrotoxicosis.

Serum protein-bound iodine. In Figure 3 are illustrated the concentrations of serum "hormonal" (protein-bound) iodine, I^{127}, as determined daily in a few typical hypothyroid, euthyroid and hyperthyroid patients.

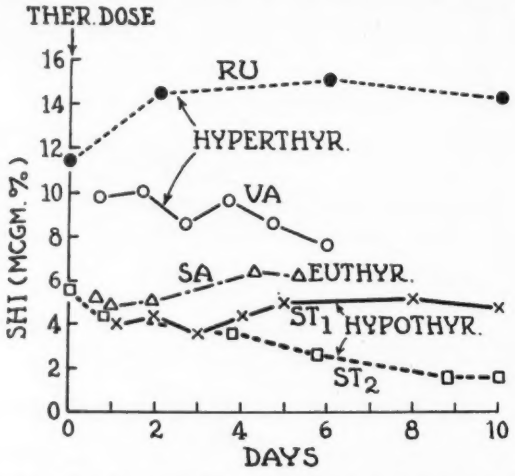

FIG. 3. In a series of selected patients showing various levels of thyroid activity (as judged clinically), the serum "hormonal" (protein-bound) iodine was determined repeatedly for several days after the administration of I^{131}. These data document the series of radioactivities shown in Table 1. Reading from top to bottom the respective dosages in millicuries (Oak Ridge, 1949 unit) were 4, 4, 5, 21 and 40 millicuries respectively. (See Table 1 and Appendix for description of the patients identified by the letters which label each curve.)

Note that conservative therapeutic dosage did not affect this concentration during the first week. A notable exception was the development of *clinical* athyreosis in patient St_2, as a tiny remnant of functioning tissue (residual after heavy dosage four months earlier) succumbed rapidly to additional heavy dosage of radioiodide, I^{131}.

Increase in serum radioactivity. Despite the constancy of stable organic ("hormonal") iodine in the serum, the specific radioactivity of the circulating hormone increased steadily. The rise in radioactivity was linear with time for several days (9). Therefore, as shown in Table 1, it was possible to measure the *rate* at which the circulating hormone became radioactive. In column 7 of the table is shown the daily increment of radioactivity (daily replacement) per 100 ml. Obviously, the more rapidly thy-

TABLE 1. REPLACEMENT OF SERUM HORMONE WITH RADIOACTIVE HORMONE

1	2	3	4	5	6	7	8	9
Patients	Dose of I^{131}		Time of measurement (days after dose)	Serum "hormonal" iodine, micrograms per cent	Relative activity fraction, F, of dose in 100 ml. serum, $\times 10^4$	Rate of activation F/day, $\times 10^4$	Relative specific activity $= \frac{SHI^{131}}{SHI^{127}}$, $\times 10^5$	$\frac{SHI^{131}}{SHI^{127}}$/day = slope
	Volume, ml.	Radioactivity, mc.						
				Hypothyroid				
St_1	4.0	49.0	3.0	2.4	0.201	0.067	0.84	0.28
St_3	5.0	21.0	5.8	2.6	0.501	0.086	1.93	0.33
Ch	0.143	0.3	1.8	2.9	0.247	0.137	0.85	0.47
Me	16.0	20.0	5.0	3.2	0.535	0.107	1.67	0.34
Ca	5.0	47.0	3.0	3.4	0.237	0.079	0.70	0.26
				Euthyroid				
St_1	10.0	21.0	5.0	4.4	1.02	0.205	2.3	0.46
La	1.32	5.0	5.0	4.6	1.26	0.250	2.7	0.54
Lo	0.15	0.066	5.0	5.4	2.05	0.41	3.8	0.76
Sa	1.50	5.0	5.3	6.2	2.06	0.39	3.3	0.62
G.He	0.1	0.097	5.0	6.8	2.33	0.47	3.4	0.68
C.He	0.1	0.097	5.0	7.1	2.43	0.49	3.4	0.68
Ce	0.05	0.26	5.0	7.6	3.20	0.64	4.2	0.84
Va	1.76	4.0	5.0	7.6	2.55	0.51	4.1	0.68
deVi	0.05	0.16	1.7	7.9	1.16	0.68	1.5	0.86
				Hyperthyroid				
Wh	0.28	5.0	5.0	8.3	2.54	0.51	3.1	0.61
Ho	0.28	5.0	5.0	8.6	3.26	0.65	3.8	0.75
$d'Al_2$	12.0	21.5	5.0	8.7	3.97	0.79	4.6	0.92
An	0.1	0.16	3.0	11.8	4.00	1.33	3.4	1.13
B	1.78	6.0	5.0	14.4	7.11	1.42	4.9	0.98
Sch	0.1	0.16	5.0	14.4	10.00	2.00	6.9	1.39
Ct	0.86	6.0	5.0	14.7	11.50	2.30	7.8	1.56
Ru	3.5	5.0	6.0	15.3	8.53	1.42	5.6	0.93
$d'Al_1$	5.0	47.0	5.0	15.6	8.15	1.63	5.2	1.04

roxine was released from the gland, the faster the serum became radioactive, as stable hormone was replaced by radioactive hormone. These rates are plotted in Figure 4 against a logarithmic function of the serum-precipitable iodine. In column 9 of Table 1, the speed of accumulating radioactivity (the replacement rate) is expressed as *specific* radioactivity (*i.e.*, related to the stable I^{127}, organically bound).

Estimation of thyroxine metabolic turnover rate (*TMR*). As shown in Figure 4, the speed at which radioactive hormone appears is nearly proportional to an "x log x" function of the protein-bound iodine. This is true despite the wide range of dosage (with I^{131}) shown in Table 1. The regularity of the blood response, together with its correlation with the functional status of the patients and the values for serum "hormonal" iodine, suggest that (even in therapeutic dosage) the serum radioactivity registers the *thyroxine*

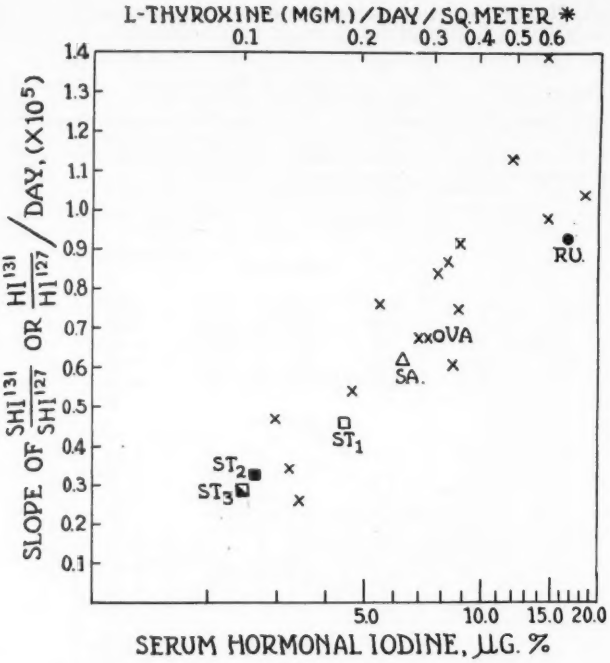

FIG. 4. The steepness (slope) of accumulating radioactivity in serum given in Table 1 constitutes a measure of thyroidal secretory activity. When plotted against serum "hormonal" (protein-bound) iodine such values form a continuous mathematical function, *i.e.*, the serum "hormonal" iodine is a good index of thyroid function.

* L-thyroxine is plotted as actual dosage, of which only about half is assimilated.

metabolic turnover rate (TMR). Elsewhere the mathematical justification for this assumption is given (9, 10). Theoretically

$$\text{TMR} = \frac{\text{Plasma volume}}{100} \times \text{SHI} \ln \text{SHI} \times k$$

$$= k \frac{\text{Serum radioactivity}}{\text{per 100 ml.}} \times \left(\frac{\text{Plasma volume}}{100} \right)^2;$$

where TMR = daily production of *l*-thyroxine (expressed as micrograms of organic iodine);

SHI = serum protein-bound iodine in micrograms per 100 ml.; and

k = the labelling constant, which is close to 0.4 in value.

DISCUSSION: APPRAISAL OF ESTIMATED THYROID FUNCTION

The foregoing method of gauging thyroid function was checked against other procedures, as follows:

1. *Conversion ratio.* Moe *et al.* (11) have made use of the *fraction* of the *total* circulating radioactivity that is protein bound. They obtained good correlation between thyroid functional status and these conversion ratios. As shown in Figure 5, the present authors have determined this index at 24-hour intervals (after dosage) and ordinarily have found the same results

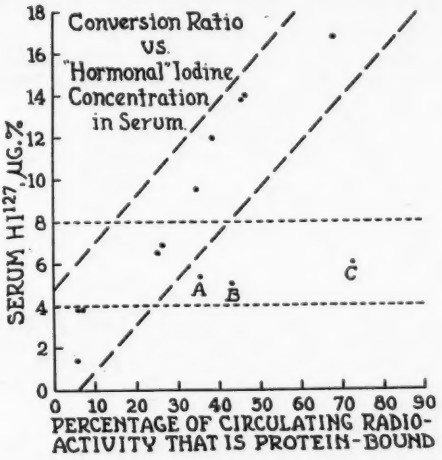

FIG. 5. Conversion ratios for 13 patients. Note that 3 patients are not in line with the others. All 3 (A, B and C) were euthyroid, with nontoxic goiters.

as Clark and his co-workers. In cases of nontoxic goiter, however, abnormally high ratios were encountered when plotted against the serum protein-bound ("hormonal") iodine, as shown in Figure 5 (points A, B and C). Therefore, the conversion ratio was abandoned as a means of checking our estimates of thyroxine metabolic turnover rate.

2. *l-Thyroxine requirements of athyreotic individuals.* A more direct check was obtained by determining experimentally the thyroxine requirement of athyreotic individuals at various equilibrium levels of metabolism (12). As shown in Figure 6, the oral requirement of *l*-thyroxine is about the same as that for racemic thyroxine, parenterally administered. For instance, in a patient with a serum "hormonal" iodine level of 7.4 micrograms per cent, the estimated TMR was about 160 micrograms per day (in terms of iodine). The parenteral daily injection of *l*-thyroxine gave a value of about 200 micrograms of iodine in the form of the *l*-isomer; and the oral administration, a value of about 240. Probably only about half of orally

administered thyroxine is absorbed (12): therefore, these three values are not inconsistent.

3. *Comparison with serum organic iodine and with thyroid pickup.* In a general way, the thyroxine turnover in the blood should be proportional to the serum "hormonal" (protein-bound) iodine concentration, as stated in the equations presented above. The value should agree also with estimates based upon the gland's turnover of the isotope, as described elsewhere (4, 13). In Table 2 are given for 3 patients the estimates for daily thyroxine turnover (TMR) based upon the three types of measurement.

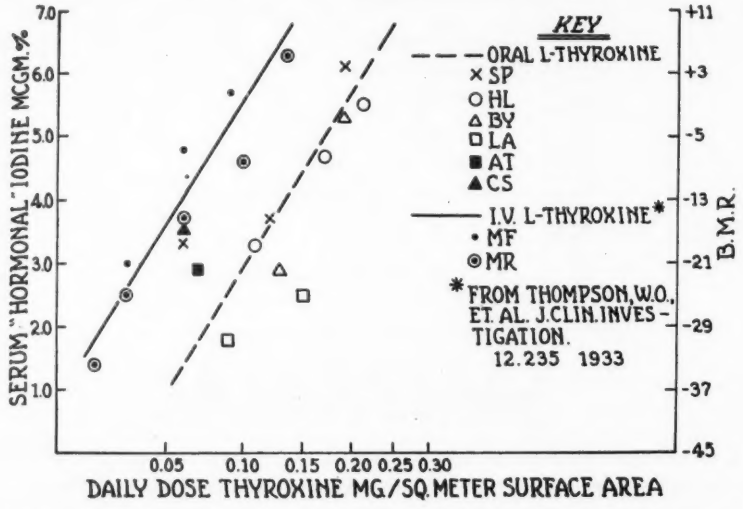

FIG. 6. Data of Rosenblum (12), combined with those of W. O. Thompson, relating serum "hormonal" iodine to thyroxine requirements. The initials indicate totally athyreotic patients described by the investigators cited.

4. *Calculation from radioactive precursor.* The rigorous and elegant mathematical approach of Zilversmit (14) proved impractical, because the accurate determination of the concentration and specific radioactivity of the precursor of the circulating thyroid hormone presents several difficulties, both analytical and theoretical. This is especially true if many "routine" determinations are undertaken.

CONCLUSIONS

If overwhelming doses of radioiodide (I^{131}) are avoided, the functional status of the human thyroid gland is not appreciably altered during the first week after conservative therapeutic dosage with the isotope. The thyroid clearance is the same as found for glands not treated with radioactive iodide; and the thyroxine metabolic turnover rate (TMR) is the

TABLE 2. COMPARATIVE VALUES FOR TMR

Patient	Thyroid status	Serum "hormonal" iodine, micrograms %	TMR (mg./24 hrs./sq.M.) as *dl*-thyroxine		
			Predicted from serum "hormonal" iodine	Estimated by radioactivity of	
				Serum	Thyroid gland
Sa	Euthyroid	5.6	0.23	0.26	0.33
Va	Borderline, euthyroid	7.5	0.30	0.31	0.31
Va	Mild hyperthyroid	12.6	0.53	0.53	0.55
	Arbitrary "normal" range	4.0 to 8.0	0.18 to 0.32		

same as with test doses. Consequently, test doses of I^{131} afford a reliable preview of the fate of conservative therapeutic doses over a wide range of thyroid activity.

Acknowledgment

The authors wish to thank Mrs. Katherine H. Barhydt for the preparation of this manuscript. They are indebted also, to Smith, Kline & French Laboratories for the levorotatory thyroxine used to treat the athyreotic patients.

APPENDIX: CENSUS OF CASES

St. *New Haven Hosp. #C43952:* white female, aged 51. Heavy x-ray therapy for "Hodgkins disease" of left cervical lymph nodes (Dr. McKittrick) more than fifteen years previously. Recent adenocarcinoma of left breast with local metastases. Moderate swelling of thyroid for eighteen years. Five years before admission, localized swelling in right upper pole of thyroid, subsiding gradually during iodide therapy. Four years later, gradual enlargement in same locus. Surgical removal of adenocarcinoma of thyroid, followed by extension of residual tissue to base of neck (left anterior). Treated repeatedly (at 3-month intervals) with radioiodide (I^{131}) in doses of 17 to 50 millicuries.

Ch. *New Haven Hosp. #C51033:* white female, aged 72. Diffuse nontoxic goiter. Cardiac decompensation of three years' duration. For six months, substernal pain and paroxysmal nocturnal asthma. No exophthalmos; BMR +51 per cent. Suspected of thyrotoxicosis and treated for half a year with 400 mg. of propylthiouracil daily; in addition, digitalized.

Me. *New Haven Hosp. #C41902:* white female, aged 56. For one year, increasing enlargement of thyroid gland, unilaterally asymmetrical. After ten months, metastatic enlargement of lower left lateral cervical lymph node. Operation disclosed papillary adenoma of left thyroid lobe with local metastases. Treated with 20 millicuries of radioiodide, I^{131}.

Ca. *New Haven Hosp. #C49256:* white female, aged 54. Enlargement of left thyroid lobe for four months. After three months, surgical removal of solitary nodule, left lobe. Pathologic diagnosis—adenocarcinoma. Two weeks later, surgical removal of left lobe, isthmus and half of right lobe. Treated twice at 2-month intervals with radioiodide (I^{131}) in doses of 36 and 40 millicuries, respectively.

La. *New Haven Hosp. #C24469:* white male, aged 51. Eighteen months before admission, onset of nervousness, exophthalmos and tachycardia, with 20-pound weight loss. BMR +55 per cent. After one year of treatment with propylthiouracil (150 to 300 mg. daily) BMR +26 per cent, with persistent exophthalmos. Treated with 3 millicuries of radioiodide, I^{131}.

Lo. *Norwalk Hosp. #95750:* white female, aged 55. Euthyroidism and diabetes mellitus (chronic), with nervous symptoms suggesting masked hyperthyroidism. Final diagnosis; no thyroid disturbance. Early BMR +17 per cent.

Sa. *Newington Vet. Hosp. #54651:* white male, aged 30. Chronic Graves' disease in euthyroid phase. Hyperthyroid two months previously, after two years of fluctuating activity. Moderate exophthalmos; labile pulse; BMR +9 per cent.

G.He. *New Haven Hosp.* (private patient of Dr. John Heller): white female, aged 45 . Menopause. Nervousness, increased appetite, cracking of fingernails; no goiter, no weight loss; preliminary BMR +35 per cent.

C.He. *New Haven Hosp.* (private patient of Dr. John Heller): white female, aged 15. Delayed puberty; polyglandular syndrome. Obesity, with cutaneous striae about hips and pigmentation of skin. BP 145/95 mm. Hg; BMR −20 per cent; 17-ketosteroids 11 mg./24 hrs.; no goiter.

Ce. *New Haven Hosp.* (private patient of Dr. John Heller): white female, aged 30. Hypochromic anemia, with dyspnea on exertion, moderate weight loss, and insomnia. No goiter. BMR normal.

Va. *Hartford Hosp. #671-501:* white female, aged 29. For one year patient has had increasing nervousness, irritability and swelling of the neck. Slight exophthalmos; weight loss of 15 pounds; BMR +34 per cent. Treated with small amounts of propylthiouracil without noticeable improvement. Propylthiouracil discontinued because of untoward reaction. Treated with 5 millicuries of radioiodide, I^{131}.

deVi. *New Haven Hosp. #C54521:* white female, aged 66. Arteriosclerosis, cardiac and cerebral. Cardiac decompensation for three years; treated with digitalis. Six months before admission, diffuse but asymmetrical enlargement of goiter of fifteen years' standing. Increasing nervousness followed, with delirium and return of decompensation (edema of legs). Serum "hormonal" iodine, 12 micrograms per cent. Treated with 3 millicuries of radioiodide (I^{131}) repeated twice at 2-week intervals. Marked diminution in thyroid size occurred, and patient improved markedly.

Wh. *New Britain Gen. Hosp. #187470* (Dr. John Larkin): white female, aged 36. Primary Graves' disease. Treated with radioiodide four months previously.

Ho. *New Britain Gen. Hosp. #184099* (Dr. John Larkin): white female, aged 34. Primary Graves' disease. Treated with radioiodide four months previously.

d'Al. *New Haven Hosp. #C49956:* white female, aged 70. Diabetes mellitus. Arteriosclerotic heart disease (compensated under digitalis therapy) and obesity. One year before admission, nodular goiter (ten years' duration) suspected of being toxic. After six months, hard nodular mass palpated in right thyroid lobe. Subtotal thyroidectomy revealed papillary adenoma of thyroid, with local metastases to lymph nodes. Despite external radiation, metastases developed in left lateral cervical chain and there was mediastinal extension on right. Treated with 25 to 47 millicuries of radioiodide (I^{131}) at 3-month intervals.

An. *Waterbury Hosp. #241656:* white female, aged 34. Recurrent thyrotoxicosis (exophthalmic goiter) following external radiation therapy thirteen years previously; had I^{131} treatment six months previously. BMR −1 per cent on January 29, 1951 (time of present study), but value doubted because of obvious clinical toxicity.

B. *Hartford Hosp. #681-038:* colored female, aged 66. History of thyrotoxicosis

without exophthalmos but with diffuse goiter, nervousness and tremor for eight months. Weight loss of 11 pounds and BMR +47 per cent.

Sch. *Norwalk Hosp. #93140:* white female, aged 40. Two previous operations for hyperthyroidism. Third recurrence of thyrotoxicosis in primary Graves' disease (exophthalmic goiter) two years after previous attack. BMR +49 per cent.

Ct. *Hartford Hosp. #677-976:* white female, aged 43. Two years before admission the patient began to lose weight. Following diagnosis of hyperthyroidism, treated with propylthiouracil for six months; twice discontinued because of loss of hair. Six months before entry symptoms recurred. Diffuse moderately enlarged goiter and tremor but no exophthalmos. Further weight loss of 18 pounds. BMR +40 per cent. Treated with 5 millicuries of radioiodide I^{131}.

Ru. *New Haven Hosp. #A69722* (Dr. Paul Lavietes): white male, aged 44. Classic thyrotoxicosis of Graves' disease for nearly three years, with alternating remissions and exacerbations. Diffuse goiter with marked exophthalmos. BMR ranged from +58 to +9 per cent, usually at +40 per cent during continued treatment with propylthiouracil (up to 300 mg. daily). Treated with 5 millicuries of radioiodide (I^{131}), repeated after two weeks.

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EVALUATION OF THE CONVERSION OF RADIOACTIVE INORGANIC IODINE TO PROTEIN-BOUND IODINE AS A DIAGNOSTIC AID IN THYROID DYSFUNCTION*

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THE diagnosis of hyperthyroidism or hypothyroidism in borderline cases is always difficult with the clinical and laboratory facilities available to most physicians. When hyperthyroidism is manifest in signs and symptoms, the disease is apparent and further laboratory work is not necessary to establish a diagnosis. There are many hypermetabolic diseases which mimic hyperthyroidism, but their etiologies are quite independent of thyroid dysfunction. The presence of hypometabolic situations is common in connection with many diseases, only one of which is hypothyroidism. Much of Kansas is in a goiter belt, thus local physicians are frequently called upon to establish a diagnosis in a patient with gross thyroid abnormality and hyper- or hypometabolic symptoms and signs, yet with normal thyroid function.

The laboratory study of the various metabolic abnormalities has been extensive, but an accurate simple procedure, perhaps a routine procedure, to evaluate thyroid dysfunction is not currently available to the practicing physician. The popular laboratory tools are the basal metabolic rate and blood cholesterol values. Each test has a wide range of normal results as well as great overlapping in borderline cases. Each of these tests is influenced by many pathologic and normal situations, entirely unrelated to thyroid abnormality. These laboratory aids are, therefore, often not reliable enough to establish a diagnosis.

The values obtained by the chemical determination of circulating protein-bound iodine in the serum or plasma display a high degree of correlation with the clinical evidence of thyroid disease. There are few situations that alter the concentration of circulating protein-bound iodine other than thyroid secretory dysfunction. This determination, however, is extremely difficult and expensive and there are many technical pitfalls. In order to obtain routinely reproducible results, a separate laboratory with its isolated equipment and highly skilled and experienced personnel is essential. This technique will probably never become available to large numbers of

Received for publication April 10, 1951.

* Aided in part by U. S. Public Health grant-in-aid H 695 C.

patients due to the financial consideration in maintaining such laboratory procedures.

Use of radioactive iodine to evaluate thyroid function has been studied extensively in the last few years, and represents a decided advance in laboratory aids. There are many advocates of the urinary excretion method. The results seem regularly valuable and accurate for the most part. However, the validity of urinary excretion data has been questioned (1). Poor correlation exists between the total amount of excreted iodine and the radioactive iodine content of the thyroid, as measured by external counting of activity in the gland (2). Other workers have not been able to correlate the administered dose with the sum of excreted iodine and that in the thyroid removed totally by surgery (3). Further disadvantages of the urinary excretion procedures are the wide overlapping of values in borderline hyperthyroid and hypothyroid patients and euthyroid persons (4). Moreover, the accurate and regular collection of radioactive urine from patients is possible only in institutions where special facilities are available.

The rate of uptake of radioactive iodine by the thyroid gland has received considerable attention recently and preliminary reports indicate that it has real diagnostic value. It does require rather rigid standards in equipment and personnel. This paper reports a method of measuring the rate of conversion of serum radioactive inorganic iodine into protein-bound iodine. Early workers in the field have shown that serum protein-bound iodine, when carefully assayed, probably represents circulating thyroid hormone (5). Thus, the measurement of the rate of conversion of inorganic radioiodine to protein-bound iodine in the serum is suggested as a method of determining thyroid hormonal function.

Much has been recorded of the whole blood and whole plasma concentrations of radioiodine after administration of a tracer or therapeutic dose (6, 7, 8). A few workers have reported the distribution of radioiodine in inorganic and various organic fractions of plasma or serum (5, 9, 10). To the author's knowledge, no report has been made of rates of appearance of thyroxine and diiodotyrosine containing radioiodine, in the blood of euthyroid persons or patients with thyroid abnormality.

The purpose of this study was to evaluate the conversion ratio of inorganic radioiodine into protein-bound radioiodine as a diagnostic tool in patients with thyroid dysfunction (4). It was also considered important to correlate the protein-bound radioiodine concentration with other iodine-containing compounds commonly found in serum and to measure the rates of appearance of each of the compounds. In addition, protein-bound iodine and total protein were determined chemically. In this manner, it was hoped to establish that circulating protein-bound iodine actually represents circulating thyroid hormone.

METHODS OF STUDY

Eighty patients were studied. Each patient was first reviewed by the medical service and given a tentative clinical diagnosis on the basis of history, physical examinations and laboratory studies consisting of basal metabolic rates and serum cholesterol values. Each patient was subsequently checked according to clinical response to appropriate treatment.

All patients studied were forbidden to ingest compounds containing thiocyanate, thiouracils, sulfonamides, desiccated thyroid, thyroxine, iodides or bromides, as each of these compounds influences the utilization of iodine by the thyroid.

Concurrently with these laboratory studies, each patient received a tracer dose of 100 microcuries of radioiodine (I^{131}) in the form of potassium iodide. This represents about 0.0001 microgram of elemental iodine.

At hourly intervals a 3-cc. sample of heparinized venous blood was drawn over a period of thirty hours and then at 24-hour intervals for six days. The plasma was promptly separated off by centrifugation at 2,500 RPM for ten minutes. The plasma was placed in a deep-freeze unit ($-4°$ C) until radioactive iodine distribution studies were performed.

Total urine samples were collected at eight, sixteen, twenty-four and thirty hours and then at 24-hour intervals for six days after ingestion of radioactive iodine. Urine samples were preserved with toluene.

Total urine radioiodine activity was measured and calculated in terms of the percentage of the ingested dose. The total plasma radioiodine activity in each sample of plasma was separated into protein-bound thyroxine, diiodotyrosine and inorganic radioiodine. All samples assayed were in the final form of silver iodide uniformly dispersed on a disc of Whatman No. 42 filter paper by collection over a water suction filter.

The radioactivity of each sample was counted with a TCG-1 Tracerlab Gieger-Mueller tube, using identical geometry for each sample. A Tracerlab 64th scaling circuit was used to record the counts.

Techniques

Total urine radioiodine activity was measured by taking a filtered aliquot of each specimen, alkalinizing to pH 8 with NaOH and filtering. The iodine was precipitated with a solution of silver nitrate containing about 5 mg. of the salt.

The treated urine was then collected on a filter paper disc (No. 42 Whatman) on a modified candle filter described previously (11). An aliquot of an exact duplicate of the administered dose previously set aside was treated in the same manner. In this way the percentage of the administered dose that was excreted was calculated. It has been found possible regularly to recover known amounts of radioiodine in the urine of a wide variety of persons with an error of ± 13 per cent.

Each blood sample was separated into a protein and a protein-free fraction by the

method of Folin-Wu. The precipitate was washed three times with water and the wash water added to the protein-free portions. The precipitate was suspended and extracted for thirty minutes with 100 cc. of normal butanol and the pH adjusted to 4 with HCl. The butanol extract was washed twice with 75-cc. portions of a solution of 5N NaOH containing 5 per cent sodium carbonate. The butanol extract contained the thyroxine-like compound (9).

The separated fluid plus the washings from the sodium hydroxide carbonate washings of the butanol extract were treated with an excess of saturated silver nitrate, as was indicated when a drop of the solution gave a red color when placed on a piece of filter paper treated with a drop of saturated potassium dichromate. The silver iodide was collected upon a candle filter as previously described.

The protein precipitate was dissolved in 4 cc. of 20 per cent (by volume) H_2SO_4. The same volume of acid was added to the butanol extract of the protein. These portions were placed in cotton-stoppered tubes and autoclaved for five hours at 130° C. and a pressure of 20 pounds, in order to digest organic iodide to inorganic iodide. Then 10 cc. of 10 per cent NaOH was cautiously added to each sample, followed by an excess of saturated silver nitrate as just described. These precipitates were collected on a filter paper in a candle water-suction filter.

To determine the protein-bound iodine conversion ratio for ingested radioactive iodine a duplicate sample of plasma was precipitated by the Folin-Wu method. Inorganic iodine was precipitated from the protein-free filtrate with saturated silver nitrate and collected on a candle filter. The entire protein precipitate was dissolved with 4 cc. of 20 per cent (by volume) H_2SO_4 and autoclaved as previously indicated. The digested sample was neutralized with 10 cc. of 10 per cent NaOH and iodides again precipitated with saturated silver nitrate.

In this way techniques designed to separate diiodotyrosine and thyroxine from inorganic iodine were compared with a previously reported procedure for simply separating protein-bound from inorganic iodine.

Thyroxine radioactive iodine is determined from the radioactivity found in washed butanol extract of plasma proteins. The diiodotyrosine radioactive iodine is found as the activity in the plasma protein-free supernatant fluid after precipitation of inorganic iodine plus the difference between total activity in the unextracted protein precipitate and the butanol extract of the protein precipitate. This method is necessary because variable amounts of thyroxine are precipitated along with plasma protein by the Folin-Wu technique.

Basal metabolic rates were determined, using a Sanborn basal metabolism apparatus (Model E-I-S) according to standard procedure (12).

Serum cholesterol values were determined according to the Lieberman-Burchard color reaction method described by Bloor (13).

Total protein values were determined by the copper sulfate falling-drop technique described by Rivers (14).

The protein-bound iodine was determined chemically by the author's method, previously described (15).

RESULTS

The urinary excretion curves of ingested radioactive iodine for the three types of patients studied are shown in Figure 1. Euthyroid patients excreted, on the average, 43 per cent of the administered dose of radioiodine in twenty-four hours and about 80 per cent by the end of six days. Hypo-

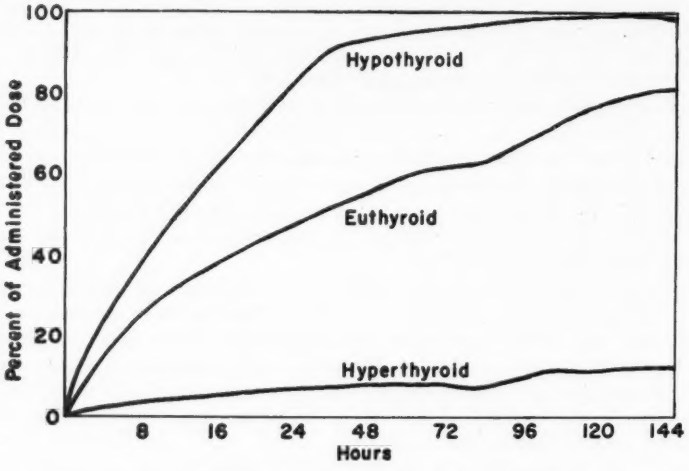

FIG. 1. Average urinary excretion of radioiodine of 72 persons with and without thyroid abnormality. The values shown represent per cent of administered dose excreted as determined periodically during a 6-day period. Ages range from 14 to 76 years.

thyroid patients excreted about 88 per cent in twenty-four hours on the average, and reached a maximum excretion of 97 to 99 per cent in about seventy-two hours. Thyrotoxic patients excreted about 8 per cent in twenty-four hours and at the end of six days had excreted only 14 per cent, on the average. The values represent total urine radioiodine activity, no attempt being made to partition urinary iodine into inorganic and organic components.

Figures 2 and 3 summarize the studies on the plasma of 20 clinically euthyroid persons (13 to 83 years of age) twenty-four hours after ingestion of 100 microcuries of radioactive iodine. Figure 2 shows that the chemically determined protein-bound iodine values in these euthyroid patients ranged from 3 to 10 micrograms per 100 cc. The total protein values ranged from 6.2 to 7.9 Gm. per 100 cc. Figure 3 shows that the percentage of total plasma radioiodine that was present as protein-bound iodine in the euthyroid patients varied from 15 to 43 per cent. The percentage of thyroxine

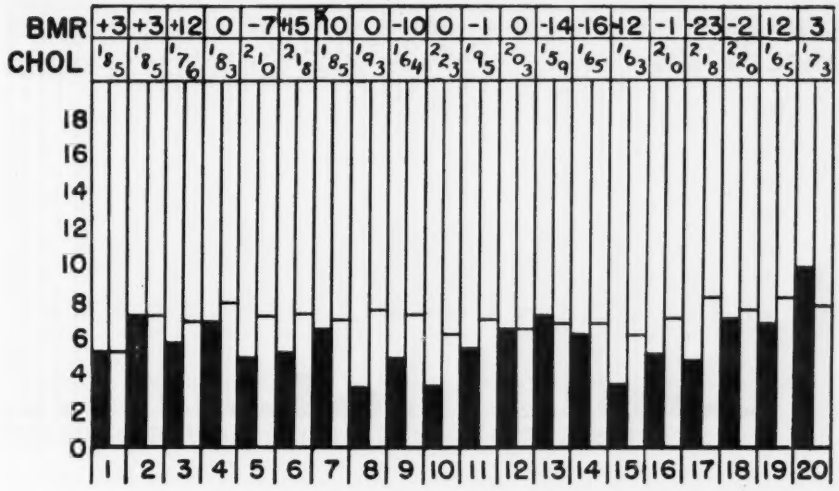

FIG. 2. Twenty patients, clinically euthyroid, without complaint or physical abnormality. Ages ranged from 13 to 83 years.
Black columns—protein-bound iodine, micrograms/100 cc.
White columns—total protein, Gm./100 cc.

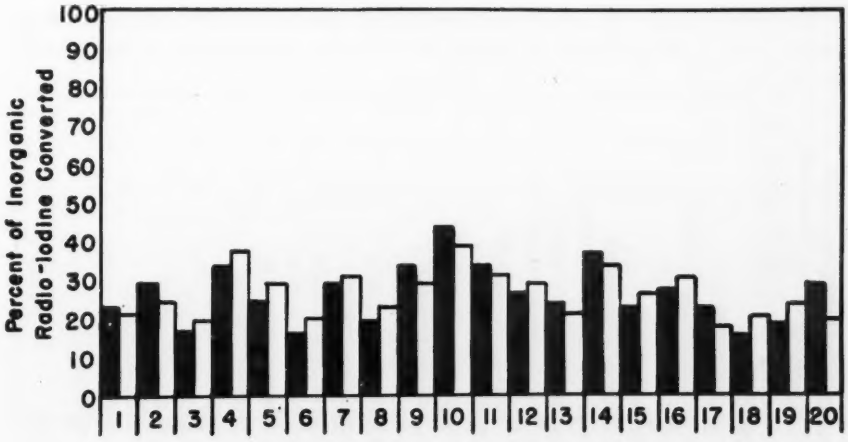

FIG. 3. Twenty patients, clinically euthyroid, without complaint or physical abnormality. Ages ranged from 13 to 83 years.
Black columns—protein-bound iodine conversion ratio.
White columns—thyroxine iodine conversion ratio.

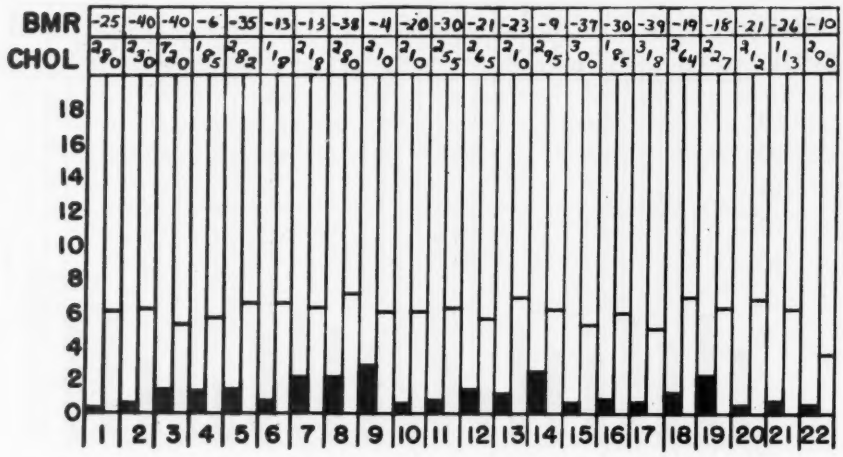

FIG. 4. Twenty-two clinically hypothyroid patients who subsequently responded to treatment. Ages ranged from 26 to 59 years.
Black columns—protein-bound iodine, micrograms/100 cc.
White columns—total protein, Gm./100 cc.

radioiodine (protein-bound iodine conversion ratio) present in the same group of patients varied from 16 to 45 per cent, the values being nearly superimposable upon the protein-bound iodine values.

Figure 4 shows the blood chemical determinations and the basal metabolic rates of 22 clinically hypothyroid patients. Patients 1–11 had under-

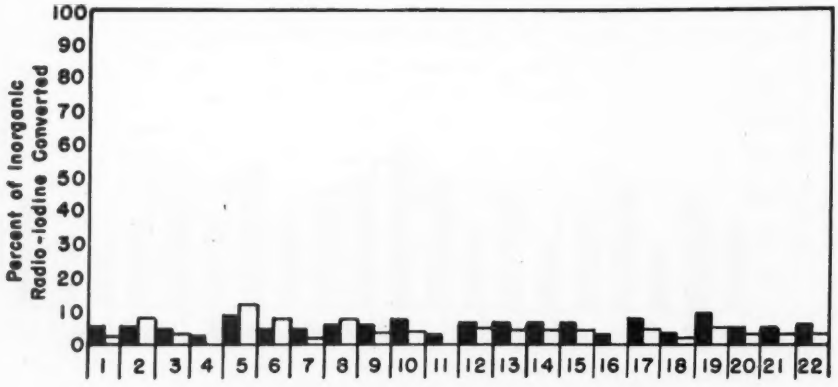

FIG. 5. Twenty-two clinically hypothyroid patients who subsequently responded to treatment. Ages ranged from 26 to 59 years.
Black column—protein-bound iodine conversion ratio.
White columns—thyroxine iodine conversion ratio.

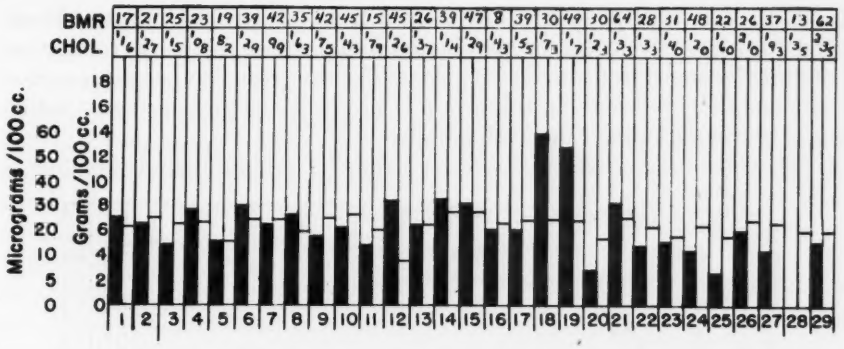

FIG. 6. Twenty-nine clinically thyrotoxic patients who subsequently responded to treatment. Ages ranged from 17 to 76 years.
Black columns—protein-bound iodine, micrograms/100 cc.
White columns—total protein, Gm./100 cc.

gone total thyroidectomy as part of treatment for thyroid carcinoma. The chemically determined protein-bound iodine values ranged from 0.2 microgram to 3 micrograms per 100 cc. Total protein values varied from 5.8 to 7.6 grams per 100 cc. Figure 5 shows that the protein-bound iodine conversion ratio in the hypothyroid patients varied from 3 to 10 per cent and the thyroxine iodine conversion ratio from 2 to 13 per cent. Once more the protein-bound iodine and thyroxine iodine conversion ratios seem superimposable.

Figure 6 reviews the blood chemical determinations and the basal metabolic rates in 29 clinically thyrotoxic patients. The chemically determined protein-bound iodine levels varied from 10 to 63 micrograms per

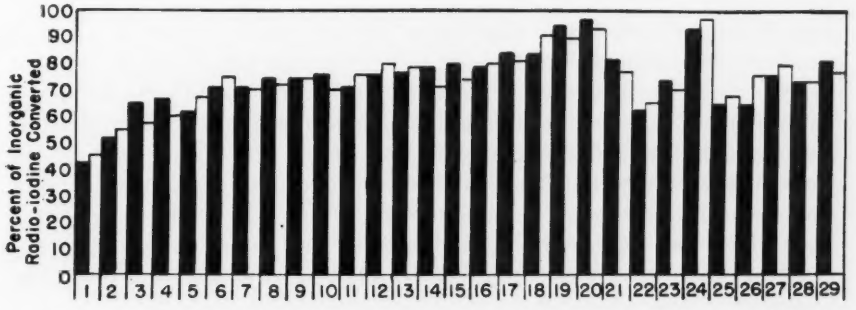

FIG. 7. Twenty-nine clinically thyrotoxic patients who subsequently responded to treatment. Ages ranged from 17 to 76 years.
Black columns—protein-bound iodine conversion ratio.
White columns—thyroxine iodine conversion ratio.

100 cc. The total protein values ranged from 5.3 to 8.1 Gm. per 100 cc. Figure 7 shows that the protein-bound iodine ratios in the thyrotoxic individuals ranged from 48 to 96 per cent. The thyroxine iodine values varied from 43 to 99 per cent. In this group of patients, the protein-bound iodine and thyroxine iodine values ran parallel.

Figure 8 summarizes the average values of protein-bound radioiodine

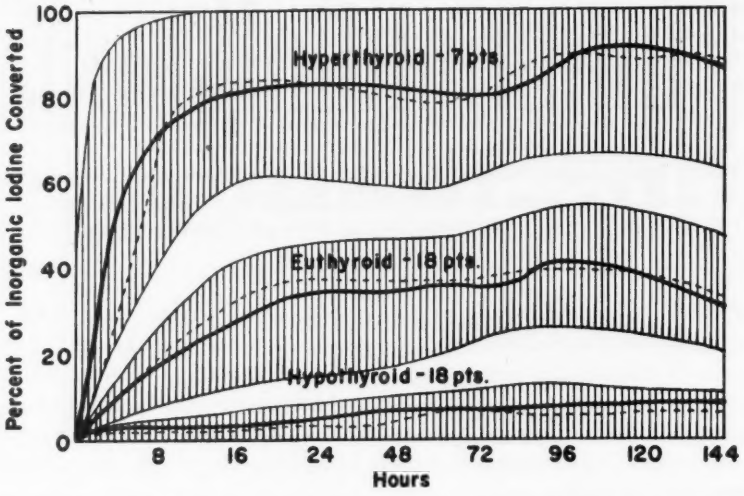

FIG. 8. Average values for protein-bound radioiodine and thyroxine radioiodine in plasma of hypothyroid, euthyroid and hyperthyroid persons. Values are recorded as per cent of total radioiodine present in sample. Experiment covers period from time of administration to six days thereafter.

---- Thyroxine % —— Protein-bound %

Shaded areas represent average deviation from mean of protein-bound iodine.

and thyroxine radioiodine through a six-day period. These levels rose slowly to a maximum of 8 per cent in twenty-four hours and 13 per cent in six days, in the hypothyroid patients. The euthyroid subjects converted an average of 31 per cent of the radioiodine into protein-bound radioiodine and thyroxine radioiodine in twenty-four hours, and 36 per cent by the end of the six-day period. The protein-bound and the thyroxine radioiodine conversion ratios reached a maximum of 80 per cent in sixteen hours, a level which was maintained through seventy-two hours. A secondary rise to 86 per cent was then maintained through one hundred and forty-four hours.

DISCUSSION

It is noted that the basal metabolic rate in the 80 patients varied widely from −35 to +80 per cent, but that it frequently did not parallel the clinical diagnosis and often ran in the opposite direction. Likewise, the

serum cholesterol level was at variance with the clinical diagnosis. These diversions are logical. The basal metabolic rate is governed by metabolic demands that originate from a wide source, only one of which is response to thyroid hormone. Circulating serum or plasma cholesterol levels are also influenced by many situations ranging from dietary habits to liver dysfunction. These determinations seem to the author to be unreliable in assessing thyroid function, unless correlated with pathognomonic signs; and these signs are frequently absent in the average patient studied.

The chemically determined protein-bound iodine regularly parallels the clinical impression and therapeutic response of patients with thyroid abnormality. It has been the impression of many workers that protein-bound iodine represents circulating thyroid hormone. The results of our study would verify this impression.

One group of workers has reported that circulating protein-bound iodine varied with the total protein concentration (16). Total protein values in the patients studied were regularly normal in the presence of a wide variation in protein-bound iodine values. In the group of patients studied, there seemed to be no relationship between protein-bound iodine levels and total protein concentration.

The conversion of radioactive iodine into protein-bound iodine regularly parallels the clinical diagnosis and clinical course of patients with thyroid dysfunction. The thyroxine iodine and protein-bound iodine are nearly superimposable, justifying the impression that protein-bound iodine measures thyroxine iodine. This is an important consideration, because of the ease of assaying protein-bound radioiodine and the relative technical difficulty of assaying thyroxine radioiodine.

SUMMARY

The protein-bound iodine of serum, whether determined chemically or assayed as conversion of inorganic radioiodine into protein-bound radioiodine regularly parallels the diagnosis and clinical course of thyroid dysfunction.

Evidence is presented to show that assay of protein-bound radioiodine probably is an assay of thyroxine radioiodine, and is therefore a direct measure of circulating thyroid hormone.

No correlation between protein-bound radioiodine levels and total protein values were found in the group of patients studied.

The basal metabolic rates and the values for serum or plasma cholesterol did not reliably predict the clinical diagnosis in our group of patients.

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HÜRTHLE CELL TUMORS OF THE THYROID GLAND: A REPORT ON 25 CASES*

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UNTIL 1945 Morrow (1) could collect from the world literature only 22 cases of Hürthle cell tumor, and he added 1 case of his own. During the last five years only 6 cases of Hürthle cell tumor have been reported, 3 by Bakay (2), 2 by Sheiman and Kravchick (3), and 1 by Neidhardt (4).

From this scarcity of case reports most writers infer that Hürthle cell tumors are extremely rare. In our own material, however, it is encountered in about 5 per cent of all solitary tumors of the thyroid. Since there is wide disagreement in the literature not only regarding the histogenesis of Hürthle cell tumors but also regarding their prognosis and treatment, we should like to present our clinical and histologic study of 25 cases of Hürthle cell tumors which we observed during the last ten years among 2,031 surgical goiter patients.

HISTORICAL REVIEW

The first reference to these tumors was made by Langhans (5) in 1907, who applied the descriptive designation "small-alveolar, large-celled struma." He reported 5 such cases. In 2 of the cases there were metastases to lung and liver, with subsequent death; the other 3 cases with unknown outcome were regarded by Langhans as also carcinomatous. No microscopic evidences of malignancy, not even invasion of blood vessels, were present in any of his 5 cases. Langhans aptly noticed the resemblance of the tumor cells to the parenchymatous cells of the liver and adrenal gland and he stressed the distinctive structure of these tumors by saying, "One glance through the microscope suffices to establish the diagnosis."

Getzowa (6) called these tumors "struma postbranchialis" and claimed that they arise from the ultimo-branchial bodies, a view which although held possible by Langhans, was considered as unwarranted by Wegelin (7). The latter maintained that the oxyphilic cell does not represent a distinct

Received for publication June 14, 1951.

* Read at the Annual Meeting of the American Goiter Association, Columbus, Ohio, May 26, 1951.

This article will be included in the bound volume of the "Transactions of the American Goiter Association" published by Charles C Thomas, Publisher, which will be available for sale early in 1952.

anatomic entity but rather a functional variant of the thyroid epithelium. This is supported by his observations that an area of large cell adenoma may be present in the center of an otherwise usual type of thyroid carcinoma, and that all stages of transition between the larger and smaller cell types may be seen in the same tumor. Clute and Warren (8) also noted the similarity between these oxyphilic tumor cells and certain involutionary changes in thyroid hyperplasia.

Ewing (9) is apparently responsible for having introduced the term "Hürthle cell tumor" into the literature. Under the heading "Struma postbranchialis (Getzowa), small-alveolar, large-cell adenocarcinoma (Langhans)," he described the highly specific structure of these tumors. He mentioned, without giving detailed clinical data, having examined two tumors answering this description and suggesting that the acidophilic cells might represent hypertrophic "Hürthle cells" of the thyroid alveoli. His Figure 492 is a typical example of such a tumor, and has the legend: Carcinoma of thyroid. Encapsulated. Acidophil adenocarcinoma. Hürthle cell tumor.

Hürthle (10), a German physiologist, described in 1894 a large oxyphilic interfollicular cell, "rich in cytoplasm," as part of the normal thyroid of the dog. Seventeen years before him Baber (11) had described the same cells in different laboratory animals, as "parenchymatous." According to him, these cells arise in the interfollicular spaces and migrate toward the follicles which they eventually enter and take part in the formation of colloid. Hürthle, on the other hand, believed that the interfollicular cells join the follicle wall, and contribute to the growth of the follicle. In 1932, Nonidez (12) also saw these cells in dogs and called them parafollicular cells. He reported the transformation and separation of these large cells from the follicular epithelium.

Maximow and Bloom (13) did not find any interfollicular cells in wax-plate reconstructions of human thyroids and therefore considered the so-called parafollicular cells as part of a horizontally cut follicular wall. Williamson and Pierce (14) also did not believe that interfollicular epithelium existed. Wilensky and Kaufman (15) doubted the anatomic specificity of Hürthle cells because all grades of transition can be found between large oxyphilic cells and the principal thyroid cells of Langendorff. They accepted Wegelin's view that the so-called Hürthle cell is a phase of the thyroid epithelium and represents a functional change, not a distinct anatomic unity.

Willis (16) believed the current use of the eponymic term "Hürthle cell tumor" to be trebly unfortunate: first, because there is no real evidence that the tumors are related to the cells described by Hürthle; second, because the very existence of special interfollicular cells in the thyroid is doubtful (Joll); and third, because the eponymic name is inappropiate since Baber described the same cells seventeen years before Hürthle. Al-

though, after studying the literature, one has to concede that Willis' standpoint is justified and that his proposed term "eosinophilic large-celled tumor of the thyroid" is preferable, the name "Hürthle cell tumor" is too well established in the literature to discontinue its use.

PRESENTATION OF DATA

The data are summarized in Table 1.

Sex and age: Twenty-four cases were observed in females and 1 in a male. In Morrow's survey of 23 cases, Hürthle cell tumors occurred in females much more often than in males (17 females as against 3 males). In Frazell and Foote's series (17) of Hürthle cell carcinoma, one quarter of the patients were males.

Our patients ranged in age from 28 to 67 years at the time of operation. The average age of the female patients was 50 years, and the only male in our series was 61 years old. In Morrow's review, 14 of his 20 subjects were over 40 years of age. Only 3 cases of Hürthle cell tumor of children have been reported; one was in a 12-year-old girl and the other 2 were in infants. The average age of the 27 patients of Frazell and Foote was 50 years.

Geographic and familial histories: With 2 exceptions (England and Sweden), all of our patients were born in the United States. Eight were from Kansas, 2 from Oklahoma, 6 from Missouri, and 1 each from 8 other states. We were unable to obtain a history of thyroid disease in the parents or siblings of our patients, and only 2 reported a familial history of cancer.

Clinical symptoms and duration of disease: The patients had noticed enlargement of the neck for from one month to fifty years; the average duration of the goiter previous to operation was given as nine and one-half years. Three patients had been operated on previously for toxic goiter.

Toxic symptoms were complained of by 9 of our 25 patients (36 per cent). A clinical diagnosis of exophthalmic goiter was made in 2 cases, and of toxic nodular goiter in 7. In 10 cases the clinical impression was solitary adenoma; in 2, malignant goiter; and in 4, nontoxic nodular goiter. Eleven patients received Lugol's solution preoperatively and 5 received propylthiouracil.

Operation: Bilateral subtotal resection was performed on 11 patients, and lobectomy on 13; in 1 instance metastatic lateral neck tumors were removed twice in addition to lobectomy. There were no postoperative deaths in this series.

Gross pathology: The weight of the surgical specimens varied between 9 grams and 226 grams. Sixteen weighed less than 50 grams; 5 goiters weighed between 50 and 100 grams; 2, between 101 and 150 grams; and 2 more than 150 grams. The average weight of the 25 specimens was 54.4 grams.

In 16 cases a solitary node was found (Fig. 1); in 8, two nodes were pres-

TABLE 1

Patient			Symptoms	Clinical diagnosis	Preop. treatment	Operation	Pathology		Follow-up
Case	Age	Sex					Gross	Microscopic	
1	52	F	Weight loss, tremor, nervousness 5 mos.	Toxic nodular goiter.	Sodium bromide.	8-12-41, bilateral resection.	35 Gm. In each lobe one node, 17 mm. and 12 mm., resp.	Two small- and large-alveolar Hürthle cell tumors (HCT) with invasion of capsule and vessels. Exophthalmic goiter.	10-20-50, alive and well 9 years 4 mos. postop.
2	59	F	Palpitation, nervousness, 20-lb. wt. loss in 1 yr.; dyspnea.	Nontoxic nodular goiter.	None.	8-19-41, left lobectomy.	15 Gm., 2×1.8 cm. Solitary node in left lobe.	Small-alveolar HCT; no invasion. Lymphadenoid goiter in diffuse colloid goiter.	10-10-50, alive and well, 9 years 2 mos. postop.
3	67	F	1) Loss of wt., 20 lbs. Goiter since 1940. 2) Paralysis rt. vocal cord. Gained 10 lbs.	1) Toxic nodular colloid goiter. 2) Cancer of thyroid.		1) 11-5-41, right lobectomy, 3 metas. 2) 3-16-42, left lobectomy, 3 met., rt.	1) 33 Gm.; 2 nodes, 4×2.5 mm. & 15×12 mm. 2) Left lobe with 2 nodes, metas. 2 nodes.	1) Small-alveolar and trabecular HCT, invading capsule and vessels. 2) Trabecular HCT. Nodular colloid hyperplasia. No invasion.	Died 1948, 7 years postop. No autopsy; cause of death unknown. No goiter symptoms.
4	30	F	Goiter 4 yrs. Loss of wt., 10 pounds. B.M.R.+41.	Toxic nodular goiter. Solitary adenoma, right.	Lugol's.	5-20-41, bilateral resection.	25 Gm.; large tumor rt. lower lobe, small tumor in isthmus. Sizes, 6 mm. and 4×2.8 cm.	1) Large: small-alveolar and trabecular. 2) Small: papillary, large-alveolar, with invasion of capsule.	12-14-50, alive and well, 9 years postop.
5	56	F	Goiter for 20 yrs. Nervousness and palpitation.	Nodular toxic goiter.	Lugol's.	5-8-42, right lobectomy.	125 Gm.; multinodular goiter, 8×6.5 cm.	Multiple nodes, trabecular, invasion of capsule and blood vessels. Lymph follicles in surrounding tissue.	10-22-50, living 8 yrs. 4 mos. postop. X-ray treatment elsewhere.
6	62	F	Goiter 3 yrs. Loss of weight. Nervousness, 6 mos.	Solitary adenoma.	Lugol's.	7-21-42, bilateral resection.	36 Gm.; solitary node in left lower pole, 3.2×2 cm.	Large follicular colloid adenoma with focal areas of small-alveolar oxyphilic HCT. No invasion. Lymphadenoid goiter in diffuse tissue.	Died 1949, cerebral thrombosis, at age 69, 7 yrs. postop. No evidence of recurrence.
7	46	F	Tachycardia, loss of 22 lbs., and exophthalmos. B.M.R.+33.	Exophthalmic goiter.	Iodine (?) 1 yr.	1) 5-22-30, bilateral resection. 2) 6-5-43, solitary adenoma, left lobectomy.	1) ———. 2) 12 Gm.; adenoma with follicles.	1) Exophthalmic goiter; 1 very small HCT with oxyphilic cells, trabecular and small-alveolar, no invasion. 2) Exophthalmic goiter with trabecular and papillary HCT. Invasion.	10-13-50, marked exophthalmos, large recurrence left, smaller right, 20 yrs. and 7 yrs. postop., resp.
8	43	F	Goiter 20 yrs. Pounding of heart and marked nervousness. Gained weight.	Solitary adenoma.		6-18-43, right lobectomy.	36 Gm., multiple nodes, colloid, between 2 mm. and 8 mm.	Minute trabecular and small-alveolar HCT. Colloid adenoma with areas of HCT. Invasion of capsule. Lymphadenoid goiter in surrounding tissue.	10-14-50, alive and well, 7 yrs. 4 mos. postop. Tumor of vocal cord removed 4½ yrs. postop.
9	50	F	Goiter 18 yrs. Nervousness.	Solitary adenoma.		3-14-44, right lobectomy.	26 Gm.; 3×2.5 cm.; solitary node in right lower pole.	Trabecular, small- and large-alveolar, papillary. Invasion of capsule. Medium sized acini, colloid filled, in surrounding tissue.	10-2-50, alive and well, 6 yrs. 7 mos. postop.
10	59	F	Goiter 40 yrs. Nervousness 6 yrs. Loss of 20 lbs. the preceding year.	1) ———. 2) Toxic nodular goiter.	———. Propylthiouracil. Iodine.	1) 3-14-44, left lobectomy. 2) 6-8-46, right lobectomy.	1) 95 Gm.; multinodular colloid goiter; 1 opaque node, 1×1.4 cm. (2) Multinodular colloid goiter.	1) Trabecular HCT in nodular colloid hyperplasia with lymphadenoid areas. No invasion. (2) Nodular colloid goiter. Lymphadenoid areas in surrounding tissue.	12-6-50, alive and well, 4 yrs. 6 mos. postop. Some hoarseness.
11	57	F	Goiter 15 yrs. Rapid heart and nervousness for 6 mos.	Nodular nontoxic goiter.		6-30-46, bilateral resection.	50 Gm.; large node in rt.; small node in left, 4.5 ×2.5 cm.	Invasion of capsule. Papillary and small-alveolar HCT. Few lymphocyte groups and medium sized acini in surrounding tissue.	10-16-50, alive and well, 4 yrs. 4 mos. postop. No recurrence.
12	47	F	Goiter 11 yrs. Nervousness and palpitation. Exophthalmos 3 mos.	Solitary adenoma in hyperplastic goiter.	Iodine.	10-15-46, bilateral resection.	22 Gm.; large node in isthmus, 2.3 cm.; small node in right lower lobe, 1 cm.	Invasion of capsule. Colloid large-alveolar adenoma. Focal trabecular, small-alveolar HCT. Small node: trabecular and small-alveolar HCT. Lymphadenoid goiter in surrounding tissue.	10-12-50, alive and well, 4 yrs. postop.
13	40	F	(3 ops., 1931–31–43). All	Recurrent exophthal-	Propyl-	12-2-46, right lobe			

									tissue.
13	40	F	(3 ops., 1931–31–43). All path. specimens showed exophthalmic in lymphadenoid goiter. Loss of wt. and exophthalmos.	Recurrent exophthalmic goiter.	Propylthiouracil. Iodine.	12-2-46, right lobectomy.	82 Gm.; large node in rt. upper pole, 4×2.7 cm.; small node in isthmus, 1.5 cm.	Large and small-alveolar, trabecular and papillary HCT. No invasion. Lymphadenoid and colloid areas in surrounding tissue.	10-30-50, living. Left lobectomy Jan. '49. Another tumor rt. side of neck, 4 yrs. postop.
14	45	F	Goiter 2 yrs. Palpitation. Gained weight.	Solitary adenoma.	Lugol's 2 mos.	5-15-47, right lobectomy.	27 Gm.; adenoma with thin rim of thyroid tissue, 2.8 cm.	Trabecular, small-alveolar HCT. Areas of usual large-follicular adenoma. Invasion of capsule. Some groups of lymphocytes, no epithelial proliferation in surrounding tissue.	4-17-50, alive and well, 3 yrs. postop.
15	36	F	Goiter 10 yrs. Weakness and nervousness.	Solitary adenoma.	Lugol's.	7-29-47, left lobectomy.	27 Gm.; node in left lower pole, 4×2.4 cm.	Trabecular, small-alveolar HCT. Invasion of capsule. Papilloma in surrounding tissue, with calcification. Lymphadenoid goiter in surrounding tissue. Marked colloidophagy.	12-22-50, alive and well, 3 yrs. postop.
16	44	F	Goiter 10 yrs. Nervousness and weakness.	Degenerative nodular colloid goiter.	Lugol's.	12-3-47, bilateral resection.	55 Gm.; multinodular colloid goiter; one HCT in right lower pole, 3 cm.	Papillary, small-alveolar trabecular, HCT. Smallest trabecular HCT in surrounding tissue. No invasion. Lymph follicles in nodular colloid hyperplasia.	10-11-50, alive and well, 3 yrs. postop.
17	61	M	Goiter since Oct., 1947 (?) Heart trouble. Loss of wt., 26 lbs.	Nodular colloid goiter with solitary adenoma.	Lugol's. Propylthiouracil.	1-14-48, bilateral resection.	152 Gm.; large adenoma in right lower pole, 6×5 cm.	Large-alveolar, small-alveolar in few areas, HCT. No invasion. Surrounding tissue colloid-rich, resting, no lymph follicles.	11-6-5), alive and well, 3 yrs postop.
18	62	F	Goiter since childhood. Loss of wt., 35 lbs. Rapid heart and nervousness.	Toxic colloid goiter.	Lugol's. Propylthiouracil.	5-21-48, bilateral resection.	74 Gm.; multinodular colloid goiter, nodes between 12 mm. and 2 mm.	Hyperplasia and lymphocytes in surrounding tissue. Multinodular colloid goiter. In one node, trabecular HCT invading colloid-rich area. No invasion of capsule.	12-11-50, has pain on right side of neck, no recurrence palpable, 2 yrs. 7 mos. postop.
19	50	F	Goiter several yrs. No toxic symptoms.	Solitary adenoma.		9-3-48, bilateral resection.	40 Gm.; 2 nodes in isthmus, 12 and 11 mm. Surrounding tissue grayish.	One alveolar HCT. One minute HCT without definite capsule. Invasion of capsule. Lymphadenoid goiter in surrounding tissue.	11-25-50, alive and well, 2 yrs. 2 mos. postop. Takes desiccated thyroid.
20	50	F	Goiter over 6 yrs. Nervousness.	Solitary adenoma, left.	Lugol's.	5-13-49, left lobectomy.	226 Gm.; large solitary adenoma, 1.5×7 cm.	Alveolar HCT. Invasion of capsule. Lymphadenoid goiter in surrounding thyroid tissue.	11-6-50, alive and well, 1 yr. 6 mos. postop.
21	47	F	Goiter 5 yrs.	Solitary adenoma.	Sodium bromide.	5-24-49, left lobectomy.	132 Gm.; two adenomas, 6 cm. and 2.2 cm.	1) Large HCT, small- and large-alveolar. 2) Small HCT, small- and large-alveolar.	10-15-50, alive and well, 1 yr. 5 mos. postop.
22	28	F	Goiter 1 mo.	Solitary adenoma.		6-30-49, right lobectomy.	9 Gm.; 1.5 cm.; solitary node 15 mm., in right lower pole.	Trabecular HCT; invasion of capsule. Well filled acini; no proliferation; no lymphocytes in surrounding thyroid tissue.	10-11-50, alive and well, 1 yr. 4 mos. postop.
23	56	F	Bilateral resection for toxic g., 1930. X-ray 2 yrs. Nervousness. Recurrence, 3–49.	Solitary adenoma.	Propylthiouracil.	3-18-50, right lobectomy.	22 Gm.; solitary tumor, 4.5×3.5 cm.	Trabecular and small-alveolar HCT. Groups of large follicles with usual epithelium. No invasion. Lymphadenoid goiter in surrounding tissue.	11-21-50, no recurrence, 1 yr. 8 mos. postop.
24	58	F	Goiter 3 yrs. Pounding of heart and nervousness. Sudden increase in size of goiter, 3 wks.	Solitary adenoma, right.	Thyroid tablets.	11-25-50, right lobectomy.	23 Gm.; 3×2.8 cm. Hemorrhage in capsule of solitary node.	Trabecular and small-alveolar HCT. Invasion of capsule. Parathyroid with small oxyphilic adenoma. Lymphocytes in compressed thyroid.	Dismissed living and well, 1 mo. postop.
25	43	F	Goiter since 1940. Nervousness 4 mos. Dyspnea. Loss of wt., 9 lbs.	Solitary adenoma, malignant.		10-19-40, left lobectomy.	51 Gm.; 4×5 cm.; single node with hemorrhage.	Trabecular and small-alveolar HCT. Invasion of capsule. Lymph follicles in surrounding tissue.	Died 3-27-46, from apoplexy. No evidence of goiter recurrence, 5¼ yrs. postop.

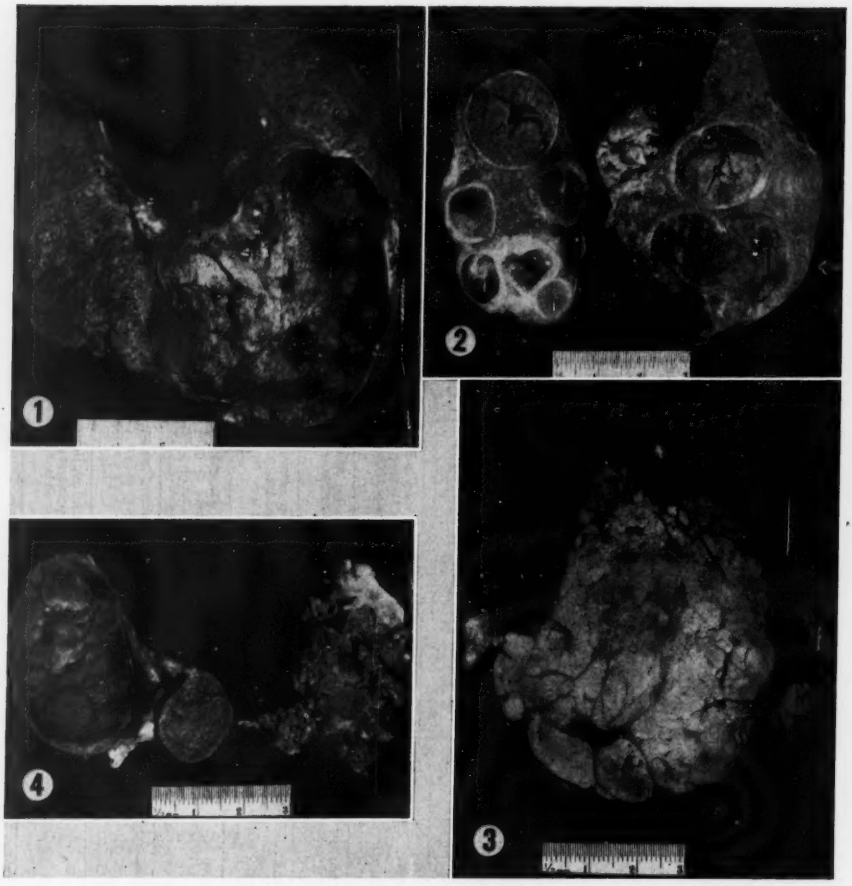

FIG. 1. (Case 17) Solitary Hürthle cell tumor. Patient living and well three years after bilateral resection of goiter.

FIG. 2. (Case 16) Hürthle cell tumor (arrow) in multinodular colloid goiter. Patient living and without evidence of recurrence, three years after bilateral resection.

FIG. 3. (Case 5) Multinodular Hürthle cell tumor involving whole right lobe. Weight 125 grams. After lobectomy local recurrence. X-ray treatment. Living now, eight and one-half years after lobectomy.

FIG. 4. (Case 3) Only cervical metastasis of Hürthle cell tumor in our series. Patient died at age 74, seven years after removal of metastatic lymph node.

ent (Fig. 2); and in 1 case there were many nodules of small size involving the whole right lobe (Fig. 3). In 6 instances the nodes were from 1 to 2 cm. in diameter; in 7, from 2 to 4 cm.; in 8, from 4 to 6 cm.; and in 4, from 6 to 8 cm. The nodes showed a grayish-brown, solid, cut surface. The cen-

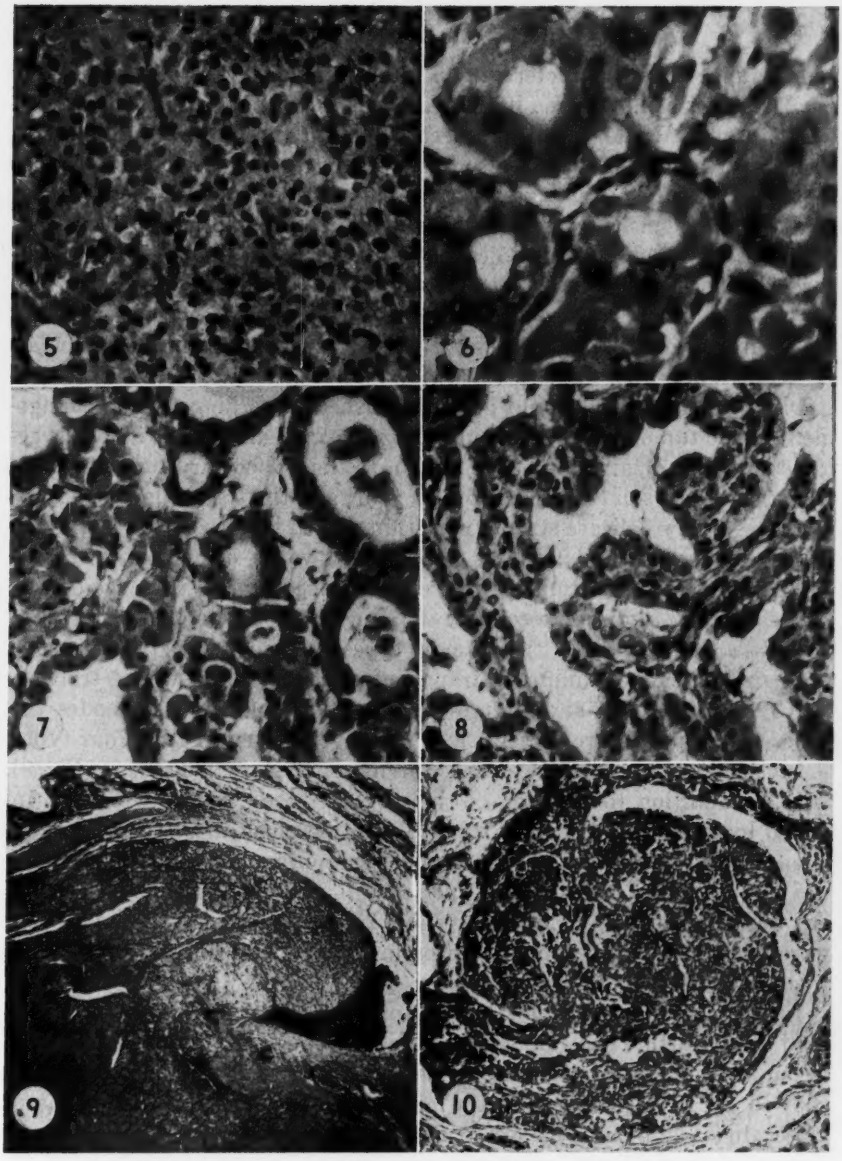

FIG. 5. (Case 18) Trabecular Hürthle cell tumor. ×240.

FIG. 6. (Case 25) Small-alveolar Hürthle cell tumor. Cytologic atypia, grade 3. ×380.

FIG. 7. (Case 21) Large-follicular Hürthle cell tumor. Cytologic atypia, grade 2. ×240.

FIG. 8. (Case 19) Papillary Hürthle cell tumor. Cell size 20 micra. ×240.

FIG. 9. (Case 5) Invasion of capsule (c) by Hürthle cell tumor. ×30.

FIG. 10. (Case 5) Invasion of blood vessel by Hürthle cell tumor. ×70.

tral hyaline scar so characteristic for fetal adenomas was absent as a rule. Small follicles could be seen in several nodes. Most of the nodes had a distinct fibrous capsule which appeared intact to the naked eye. The two metastatic nodules in Case 3 also had a smooth surface, and they did not invade surrounding structures (Fig. 4). No invasion of larger blood vessels could be distinguished with the naked eye in any of our specimens.

Microscopic findings: Our 25 cases showed the typical microscopic structure of Hürthle cell tumors. The characteristic tumor cell was polyhedral, cuboid or columnar, of very large size (15–30 micra) with abundant eosinophilic, finely granular cytoplasm, a distinct cell border and a vesicular, rather pale nucleus.

Different sub-groups could be distinguished, according to the arrangement of the tumor cells—trabecular (Fig. 5) small-alveolar (Fig. 6), large-follicular (Fig. 7), and papillary (Fig. 8). In the trabecular tumors the cells were growing in solid cords 2 to 6 cells wide, and the trabeculae were separated by a very delicate stroma with thin-walled blood vessels. In the follicular tumors, glandular spaces were formed which often contained thin colloid. The papillary tumors were characterized by the presence of thin stalks of connective tissue covered with one layer of tumor cells.

Often a combination of two or more types was encountered. Ten tumors presented an entirely uniform arrangement of cells. There were 5 trabecular, 3 small-alveolar, and 2 large-follicular tumors; but in 11 nodes two types of structure were present; in 3, three types; and in 1, all four types.

Invasion of the capsule was encountered in 12 goiters (Table 2) (Fig. 9). In 3, in addition to invasion of the capsule, blood vessels were also invaded by tumor growth (Fig. 10). No invasion of blood vessels was noted in encapsulated tumors. Mitotic figures were noticed in 3 tumors, giant nuclei in 5 and large nucleoli in 9. Variation in size and form of cells and nuclei were encountered in 20 cases (Table 2). The cervical metastases which were removed at the second operation in Case 3 had a trabecular structure without marked cellular anaplasia.

In 9 of the 23 cases reviewed by Morrow, hyperthyroidism was associated with Hürthle cell tumors, and the incidence was almost the same as in our series (9 out of 25, or 36 per cent). In 9 cases the surrounding tissue showed no hyperplasia; in 4 the histologic diagnosis was exophthalmic goiter; in 8, lymphadenoid goiter; and in 4, nodular colloid goiter. It seems evident that the toxic symptoms were caused by the hyperplasia of the thyroid tissue proper and that the Hürthle cell tumor by itself had no endocrine function.

An unusually large number of goiters (20, or 80 per cent) showed nests of lymphocytes in the surrounding tissue, and 15 cases had lymph follicles with germinal centers. In our total series of 2,031 surgical goiters, lympho-

TABLE 2. PATHOLOGIC HISTOLOGY AND FOLLOW-UP RESULTS

Patient		Anisocytosis	Anisokaryosis	Hyperchromasia	Mitoses	Invasion of capsule	Invasion of blood vessels	Colloid	Cytologic atypia	General arrangement	Follow-up
Case No.	Age										
1	52	x	x	x		x	x	1+	5	Disorderly	L and well, 9 yrs.
2	59	x	x	x		–	–	1+	3	Orderly	L and well, 9 yrs.
3 a	67	x	x	x		x	x	0	5	Disorderly	
3 b		x	x	0	x			0	3	Orderly	Died
4	30	x				x		0	2	Orderly	L and well, 9 yrs.
5	56	x	x		x	x	x	0	5	Disorderly	Alive with recurr., 8 yrs.
6	62	–	–	–	–	–	–	2+	1	Orderly	Died, 7 yrs. postop.
7 a	46	x	x	–	–	–	–	0	2	Orderly	Recurrence, 13 yrs.
7 b		x	x	x	–	x?	–	0	3	Disorderly	Alive with recurr., 20 yrs.
8	43	x	x	x	–	x	–	0	4	Orderly	L and well, 7 yrs.
9	50	x	x	–	–	x	–	1+	3	Disorderly	L and well, 6 yrs.
10	59	x	x	x	–	–	–	0	2	Orderly	L and well, 4 yrs.
11	57	x	x	–	–	x	–	3+	3	Orderly	L and well, 4 yrs.
12	47	x	x	–	–	x	–	0	3	Orderly	L and well, 4 yrs.
13	40	x	–	–	–	–	–	0	1	Disorderly	Recurrence, 3 yrs.
14	45	–	x	0	0	x	–	0	2	Orderly	L and well, 3 yrs.
15	36	–	x	x	x	x	–	0	3	Orderly	L and well, 3 yrs.
16	44	x	x	x	–	–	–	1	3	Orderly	L and well, 3 yrs.
17	61	x	x	x	–	–	–	1+	3	Orderly	L and well, 3 yrs.
18	62	–	–	–	–	–	–	0	0	Orderly	L and well, 2 yrs.
19	50	x	x	–	–	–	–	0/2	2	Orderly	L and well, 2 yrs.
20	50	x	x	x	–	x?	–	3+	3	Orderly	L and well, 1 yr.
21	47	x	x	–	–	–	–	1+	2	Orderly	L and well, 1 yr.
22	28	x	x	–	–	x	–	0	3	Orderly	L and well, 1 yr.
23	56	–	–	–	–	–	–	0	0	Orderly	L and well, 1 yr.
24	58	x	x	x	–	–	–	0	3	Disorderly	L and well, 1 yr.
25	43	x	x	–	–	–	–	1+	3	Orderly	Died 6 yrs. postop.

cytes were found in 63.9 per cent. The higher incidence in Hürthle cell tumor is explained by the large number of associated lymphadenoid goiters (8) and exophthalmic goiters (4). In these two forms lymphocytes occur in 100 per cent and 92.3 per cent, respectively. The aggregations of lymphocytes or true lymph follicles cannot be regarded as a manifestation of Graves' constitution (Warthin, 18) or as characteristic of toxic goiter, since of our 16 nontoxic Hürthle cell tumors, 14 showed groups of lymphocytes, and 11 of those 14 showed lymph follicles with germinal centers.

Of interest also was the high incidence of Hürthle cells in the thyroid tissue proper surrounding the Hürthle cell tumors. They formed either small follicles with some colloid in their lumens, or formed solid trabeculae surrounded by lymphoid tissue. There were 13 cases with Hürthle cells in the thyroid tissue proper, and in 8 of these cases they were very abundant. All of the lymphadenoid goiters had Hürthle cells, as had also 2 of the 4 exophthalmic goiters.

Follow-up studies: The time of observation after operation in our cases varied between one and one-half and nine years. At present, of the 25 pa-

tients, 22 (88 per cent) are alive, and 20 (80 per cent) are without evidence of disease. Three patients are dead. One died at 74 years of age of unknown cause, seven years after surgery; 1 died at the age of 49, five and one-half years after the goiter operation, without showing evidence of metastasis or recurrence of goiter; and 1 died seven years after operation following a cerebral accident at the age of 69.

One patient had x-ray treatment of her thyroid but she is at present alive and well, eight years and four months after removal of a multinodular trabecular Hürthle cell tumor, which microscopically showed invasion of capsule and blood vessels. Another patient had the right lobe and three cervical nodes removed, which microscopically showed capsule and vessel invasion; four months later she had the left lobe of the thyroid and a metastatic node on the right side of the neck removed; she died seven years later at the age of 74. In 1930, another patient (Case 7) had a bilateral resection of an exophthalmic goiter with a small trabecular Hürthle cell tumor; thirteen years later a trabecular-follicular Hürthle cell tumor, which showed invasion of the capsule, was removed; at present, seven and one-half years after the second operation, she has a large recurrent goiter on her left side and a smaller node on the right. One patient (Case 13) had three operations for diffuse toxic goiter between 1931 and 1943; in 1946 a trabecular and papillary Hürthle cell tumor, which did not show invasion of the vessels or capsule, was removed from the right side; in January 1949, she had the left lobe removed and now a tumor is apparent on the right side of the neck.

DISCUSSION

For the goiter surgeon the most important problem is how radically should Hürthle cell tumors be treated? If we accept Harry's (19) view that all Hürthle cell tumors are adenocarcinomas of moderate malignancy, a complete bilateral thyroidectomy with radical neck dissection would be indicated. On the other hand, if we follow Wegelin's belief that most Hürthle cell tumors are benign adenomas, a removal of the tumor is all the treatment that would be necessary.

Ten of the 23 cases listed by Morrow were regarded as cases of adenoma, and 8 were regarded as cases of carcinoma; in 5 cases the tumor type was not reported. Morrow concluded that for ultimate safety it may be best to consider every Hürthle cell tumor potentially as carcinoma and treat it as such. Of the 6 cases of Hürthle cell tumors reported since Morrow's review: the 3 cases of Bakay were diagnosed as adenomas; Sheiman and Kravchick's first case was regarded as a carcinoma and the second as an adenoma (both patients died a short time after operation); Neidhardt regarded his case as a low-grade adenocarcinoma but the patient was not fol-

lowed. Clute and Warren, in a review of 226 cases, found 1 case of Hürthle cell adenocarcinoma, but they did not report any clinical data.

Reviewing 27 Hürthle cell carcinomas, Frazell and Foote found chest metastases in 3 of 11 previously treated patients and metastases to cervical lymph nodes in 6 of 13 untreated cases. In 5 of their patients osseous metastases occurred. The authors conclude that Hürthle cell carcinomas are of a fairly high grade of malignancy; only one third of their patients were alive and free of disease five years after diagnosis. They advised a radical approach, including neck dissection, for this type of malignant goiter.

In a personal communication Foote stated that in his experience there

TABLE 3. RELATION OF HISTOLOGIC FINDINGS TO CLINICAL FOLLOW-UP RESULTS IN 25 CASES OF HÜRTHLE CELL TUMOR

	Histologic findings			
	Capsule intact	Invasion of capsule	Invasion of blood vessels	Involvement of cervical lymph nodes
Living and well:	8	11	1	
Recurrence:	1		1	
Died:	1 (7 yrs. p.o.)	1 (5½ yrs. p.o.)	1 (7 yrs. p.o.)	1
Totals	*10*	*12*	*3*	*1*

exist two general types of Hürthle cell carcinomas, one of which is very orderly in structure, and the other disorderly in nuclear and cellular make-up. Some of the very orderly Hürthle cell carcinomas will develop metastases as long as eight years after removal of the thyroid mass, and on several occasions Foote found that the metastatic lesions looked microscopically exactly like the seemingly innocent primary tumor. The vast majority of the orderly Hürthle cell tumors, according to Foote, run a benign clinical course. Foote makes a diagnosis of Hürthle cell carcinoma when he sees vein invasion or cellular malignant changes. In regard to vein invasion, which Graham (20) regarded as the best criterion of malignancy in adenomas, we have to remember that Warren (21) found evidence of a malignant clinical course in only 6.3 per cent of his cases with blood vessel invasion.

A correlation between microscopic evidence of malignancy in Hürthle cell tumors and clinical results was not always evident in our material

(Table 3). Table 2 shows the presence of anisocytosis, anisokaryosis, hyperchromasia, mitoses, invasion of the capsule, invasion of blood vessels, the amount of colloid and general arrangement. In Case 1 the tumor showed a cytologic atypia grade 5 and a disorderly general make-up, but the patient is well nine years and four months after bilateral subtotal resection. The metastases in Case 3 were entirely orderly in general arrangement and showed only a grade 3 atypia. On the other hand all recurrences which we encountered were from tumors which had a disorderly histologic structure. There was no definite correlation between the size of Hürthle cell tumors and their clinical course (Table 4) as in hypernephroma (Bell).

TABLE 4. RELATION OF SIZE OF TUMOR TO CLINICAL FOLLOW-UP RESULTS

Diam. of tumor	No. of Cases	L & W	Metast. or recurr.	Died
Below 3 cm.	10	9	1	0
From 3 to 5 cm.	12	9	1	3
Over 5 cm.	3	2	1	0
Totals	*25*	*20*	*3*	*3*

From the study of our 25 cases, we believe that most Hürthle cell tumors behave like solitary adenomas and that in most cases a lobectomy of the involved side without neck dissection is a sufficient operation. Even if subsequent histologic study reveals invasion of the capsule or of lymph and blood vessels, a lobectomy for a solitary tumor seems adequate to us. In the presence of palpable lymph nodes, we advise removal of the enlarged nodes followed by x-ray treatment.

SUMMARY

1. During the last ten years, 25 cases of Hürthle cell tumor were observed at the Hertzler Clinic, Halstead. This type of tumor was encountered in more than 1 per cent of all surgical goiters, and in about 5 per cent of all solitary thyroid tumors.

2. Twenty-four of the Hürthle cell tumors were observed in females and 1 in a male. The ages ranged from 28 to 67 years at the time of operation. The average age of the female patients was 50 years.

3. Enlargement of the neck was noticed by these patients for from one month to fifty years. Three patients had previous operations for toxic goiter.

4. Nine of the 25 patients (36 per cent) had toxic symptoms. The latter

were caused by the hyperplasia of the thyroid tissue proper. The Hürthle cell tumor itself had no endocrine function.

5. Bilateral subtotal resection was performed on 11 patients, lobectomy on 13, and in 1 case lateral cervical nodes were removed in addition to the lobectomy.

6. The weight of the surgical specimens varied between 9 grams and 226 grams. In 16 cases a solitary node was found; in 8, two nodes were present, and in 1 case there were multiple nodules involving one lobe. Microscopically all tumors were composed of typical Hürthle cells arranged in trabeculae, follicles or papillae. Invasion of the capsule was encountered in 12 tumors; in addition to the capsule, blood vessels were also invaded in 3 tumors.

7. Of our 25 patients, 22 (88 per cent) are alive and 20 (80 per cent) are without evidence of disease, from one and one-half to nine years after thyroidectomy. One patient who, at the first operation, had metastases in the cervical lymph nodes, died seven years later at the age of 74. Two patients at present show evidence of a recurrent tumor, four and seven years, respectively, after the operation. In the fatal cases the average duration of life after operation was six and one-half years.

8. Six of 12 patients followed for more than five years postoperatively are alive and free of disease. Our over-all five-year survival rate is 75 per cent.

9. The preoperative diagnosis was benign goiter in 23 cases, and cancer of the thyroid in 2 cases.

10. Removal of the involved lobe is considered by us to be a sufficiently radical procedure for the great majority of Hürthle cell tumors. In the presence of palpable cervical lymph nodes we advise, in addition to thyroidectomy, removal of these nodes followed by x-ray treatment.

CONCLUSIONS

After studying 25 cases clinically and microscopically, we are unable to answer categorically the question whether Hürthle cell tumors are benign adenomas or true cancers.

Microscopic examination will not give a definite answer in every case, especially if the structure of the Hürthle cell tumor is orderly.

The microscopic evidence of blood vessel invasion cannot be regarded as an infallible sign of clinical malignancy. From a practical standpoint, we accept the tenet of most goiter surgeons, that Hürthle cell tumors, like any other solitary thyroid tumor, should be removed as soon as detected.

We believe that removal of the involved lobe without neck dissection will cure most cases of Hürthle cell tumors, as long as they have not spread to other parts of the body.

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THE SOMNOLENT METABOLIC RATE (SMR) AS AN AID IN THE DIFFERENTIAL DIAGNOSIS OF THYROID DYSFUNCTION*†

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DESPITE advances which have been made in our understanding of the essential nature of thyroid disease, the differential diagnosis of varying functional states often remains difficult. Much of the confusion has arisen because few objective methods have been developed to determine actual thyroid activity. In general, thorough and thoughtful clinical investigation remains a significant factor in arriving at a diagnosis.

Nevertheless, the serum cholesterol, the basal metabolic rate, the serum protein-bound iodine, as well as radioactive iodine uptake studies all have been accepted as valuable adjuncts in determining the clinical diagnosis. In our hands the blood cholesterol has not shown sufficiently consistent change to be of any real help in indicating thyroid dysfunction.

Although an elevated basal metabolic rate suggests overactivity of the thyroid gland and, more commonly, a lowered rate indicates diminished activity, it is recognized that the BMR may be affected by other factors in the presence of normal thyroid function (1, 2). "The BMR is a measurement of oxygen consumption, the end result of a great many oxidative processes, and not necessarily of that alone associated with the transport, utilization and breakdown of thyroid hormone" (3).

In a recent review of the clinical significance of the blood protein-bound iodine, we concluded that the PBI was the best available laboratory aid in the diagnosis, the appraisal of response to therapy and the prognosis of thyroid disorders (4). Others have supported this viewpoint (5–10). This test becomes of questionable value, however, when the patient has recently been receiving iodine *in any form.*

Radioactive iodine tracer studies are generally effective in determining

Received for publication June 14, 1951.

* Read at the Annual Meeting of The American Goiter Association, Columbus, Ohio, May 24, 1951.

This article will be included in the bound volume of the "Transactions of the American Goiter Association" published by Charles C Thomas, Publisher, which will be available for sale early in 1952.

† Aided by a Grant from The Comly Fund for Research of The Ohio State University.

thyroid function but these studies, too, are of questionable value in the face of excessive exogenous iodination. Moreover, the use of I^{131} is restricted to specialized centers and is not generally available even for diagnostic studies.

Many attempts have been made to correlate the BMR and the PBI (11–19). Some of these have been wholly unsuccessful. Others have resulted in the derivation of complicated formulae, none of which shows conclusive correlation. Because of this apparent disagreement many investigators have been critical of the PBI, believing that failure of correlation indicated that the latter is of no clinical significance. It has been our belief, on the other hand, that in many instances it is the BMR which gives misleading information, rather than the PBI.

It is essential that the basal metabolic rate be determined under ideal conditions of mental and physical inactivity so that the results obtained represent truly "*basal*" metabolism. In many patients this can be accomplished by rest in quiet surroundings for at least thirty minutes before the test. A competent, well-trained, sympathetic and intelligent technician is another necessity, because mismanagement of the patient can interfere significantly with the results. However, with even the best technician and under the most ideal conditions, it is impossible to produce a cessation of cerebration. Minimal emotional stress may result in a significant spurious elevation of the metabolic rate. It is in such apprehensive individuals that the differential diagnosis of thyroid disease may be most difficult.

Various measures have been utilized to produce a more basal state in such emotionally unstable patients. Serial testing in order to familiarize the patient with the technique, administration of phenobarbital for several days before the test, or the administration of nembutal the night before and again one hour before the test in the morning have been used with some success. A group of patients remains, however, in whom testing is still unsatisfactory.

Aware of these difficulties, Bartels has recently reported a series of patients in whom the BMR was determined after sleep had been induced by the intravenous administration of sodium pentothal (20). In normal patients the metabolic rate dropped an average of 13 per cent, whereas patients with hyperthyroidism showed little drop in the BMR. More significant was a group of patients with greatly elevated metabolic rates due to various nervous states, in whom the rates dropped to normal under sodium pentothal anesthesia, indicating absence of hyperthyroidism. Bartels states: "This method of metabolism testing induces a perfect basal state—the resulting rate being void of all nervous and muscular factors."

We were impressed by Bartels' report but objected to the necessity of a

trained anesthetist, cocainization of the throat and the use of a metal airway in some instances. We agree that such precautions are necessary when anesthesia is produced by sodium pentothal. It occurred to us, however, that similar "ideal" basal conditions simulating normal sleep could be achieved by the use of intravenous nembutal. Such a method would not have the inherent dangers (especially laryngospasm) of sodium pentothal and, we hoped, might be carried out as an office procedure.

We accordingly undertook the comparative testing of a series of patients, first in the routine "basal" state and then asleep under the effects of intravenous nembutal. We were interested in the effect of the nembutal on the BMR; and also were curious to know if the metabolic rate under anesthesia, as well as the blood protein-bound iodine, would correlate better with the clinical diagnosis than does the routine BMR.

METHOD

The patient to be studied is instructed to eat nothing after 10 P.M. in the evening preceding the test, is advised to get a good night's rest and is, in general, prepared as for a routine BMR. There is no premedication. At the time the appointment is made the patient is usually advised that the basal metabolic rate is to be determined while he is asleep. If the subject is especially apprehensive and there have been no previous routine determinations of the BMR to serve as a base line, there is no information given concerning the special procedure until after the basal rate has been determined in the usual manner. Effort is made to stress the benignity of the procedure. It is emphasized that the sleep produced does not approach surgical anesthesia in depth, and that ordinary conversation is sufficient to arouse the patient after the test has been completed.

Following a rest period of at least thirty minutes, two consecutive determinations of the BMR are done in the usual routine manner.[1] Blood is drawn for determination of the protein-bound iodine after completion of the second test. Blood iodines are determined by the method of Connor, *et al.*, as developed in this laboratory (21, 22).

Intravenous nembutal is then administered in a concentration of 50 mg. per cc., until the patient is asleep. The medication is fractionated by giving an initial dose of 1 cc. (50 mg.) followed by 0.5 cc. (25 mg.) per minute until sleep is produced.

Dosage. We found no method of estimating in advance the amount required for anesthesia. There was no correlation between the patient's age, sex, weight or clinical diagnosis and the amount of nembutal necessary to produce sleep. The average dose was slightly over 4 cc. (212 mg.) and in most instances varied between 1.0 cc. (100 mg.) and 6 cc. (300 mg.). Two patients required only 75 mg. and 6 required more than 300 mg. In 1 patient 500 mg. was necessary to induce sleep.

A laryngoscope, a metallic airway, an endotracheal tube and metrazol are available at all times, but we have found no occasion to use them.

After sleep is produced the rubber mouthpiece is inserted and held in position with strips of adhesive tape[2] (Fig. 1). Dentures are not removed. If the patient is edentulous

[1] All testing was done by one of the authors.

[2] A rubber mask proves less satisfactory than a mouthpiece, because of inadequate fitting in some instances.

and has no dentures the mouthpiece must be supported during the entire test in order to prevent leaks. The chin is supported to facilitate normal breathing when necessary.

Two consecutive metabolic tests are taken while the patient is asleep. He is then awakened by ordinary conversation and is allowed to return home with a relative or companion. In no instance was it impossible to awaken the patient at once. However, patients vary considerably in their ability to arise. Some are up immediately and complain only of minimal fatigue; others are quite drowsy and ask to be allowed to sleep.

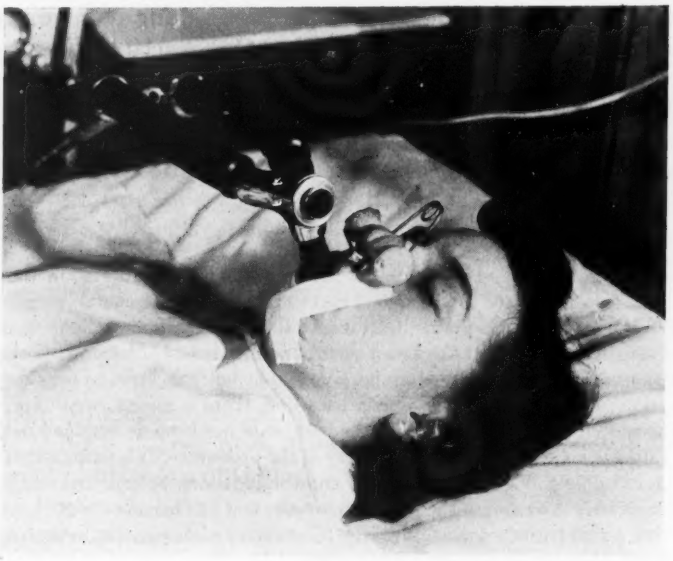

FIGURE 1

Some report no effect from the anesthesia, whereas others sleep more or less continuously until the following morning.

SELECTION OF PATIENTS

Two hundred determinations of the somnolent metabolic rate (SMR)[3] were made on 152 patients. Forty-three of these were clinically hypothyroid, 67 were euthyroid and 42 were hyperthyroid. This group is not considered typical of patients with thyroid disease, since approximately half of the patients did not initially present clear-cut symptoms and were referred to us for aid in diagnosis.

Those classified as hypothyroid included 27 cases of typical hypothyroidism, 2 cases of spontaneous myxedema and 2 cases of typical myxedema

[3] We have used this term to refer to the metabolic rate determined under intravenous nembutal anesthesia.

following thyroidectomy for carcinoma of the thyroid, as well as patients in whom there were varying degrees of disagreement initially as to the diagnosis. All patients classified as hyperthyroid, on the other hand, presented characteristic symptoms of thyrotoxicosis and included 22 cases of toxic nodular goiter, 17 cases of Graves' disease and 3 of recurrent hyperthyroidism. Those patients designated as euthyroid presented of a variety of conditions. This group contained the largest number of patients whose BMR was not compatible with the clinical diagnosis, or in whom the diagnosis was not initially clear.

RESULTS

Hypothyroidism

Fifty-one somnolent metabolic rate (SMR) determinations were made on 43 patients in this group. The results are presented in Table 1.

TABLE 1. DETERMINATION OF PBI, BMR AND SMR: SUMMARY OF RESULTS IN 43 HYPOTHYROID PATIENTS

	Number of determinations	Average results
PBI	41	2.9 mcg. %
Previous average BMR	29	− 3%
BMR Immediately preceding IVN*	51	−11%
SMR	51	−25%

* Intravenous nembutal.

The average of 41 determinations of the blood protein-bound iodine was 2.9 micrograms per cent.[4] The average of previous determinations of the BMR immediately preceding nembutal in 51 instances was −11 per cent and the average SMR in 51 instances was −25 per cent. There was an average fall of 14 points between the pre-nembutal BMR and the SMR.

The blood protein-bound iodine was compatible with the clinical diagnosis in 30 of 41 determinations (73 per cent) (Table 4). In the remainder the blood iodine was not determined or was considered invalid because of exogenous iodination. In the 11 instances in which the PBI was not compatible with the clinical diagnosis the highest value recorded was 5.5 micrograms per cent.

[4] The normal range of the PBI by the method used is 3.7 to 6.7 micrograms per cent.

Twenty-nine patients had previous determinations of the BMR, of which only 11 (38 per cent) fell below the lower level of the normal range, *i.e.*, −13 per cent.[5] Twenty-nine of 51 (57 per cent) routine determinations of the BMR preceding nembutal were compatible with the clinical diagnosis, whereas all 51 (100 per cent) of the SMR determinations were compatible (Table 4).

Euthyroidism

Seventy-four determinations of the SMR were made on 67 patients in this group. Results are presented in Table 2.

TABLE 2. DETERMINATION OF PBI, BMR AND SMR: SUMMARY OF RESULTS IN 67 EUTHYROID PATIENTS

	Number of determinations	Average results
PBI	53	4.6 mcg. %
Previous average BMR	42	+16%
BMR Immediately preceding IVN*	74	+13%
SMR	74	− 2%

* Intravenous nembutal.

The average of 53 determinations of the PBI was 4.6 micrograms per cent. The average of previous determinations of the BMR in 42 instances was +16 per cent, the average BMR immediately preceding nembutal in 74 instances was +13 per cent, and the average SMR in 74 instances was −2 per cent. There was an average fall of 15 points between the BMR preceding nembutal and the SMR.

The blood protein-bound iodine was compatible with the clinical diagnosis in 39 of 47 determinations (83 per cent) (Table 4). In the remainder the blood iodine was not determined or was not considered valid because of exogenous iodination. Of the 8 values for the PBI which did not agree with the clinical diagnosis, 3 were above the range of normal. In 2 of these the SMR was within the normal range, and in the third the SMR was plus 9 per cent. Five of the values for the PBI were below the range of normal.

[5] Normal range of the basal metabolic rate is determined as follows: Normal range = normal average, ±1 per cent, S.D.; or, normal range = −5 per cent ± 8 per cent, or, from minus 13 per cent to plus 3 per cent for Central Ohio (7).

In 4 of these the SMR was in the normal range and in the fifth it was plus 4 per cent.

Forty-two of these patients had previous determinations of the BMR of which only 12 (29 per cent) fell within the normal range of −13 to +3 per cent. Twenty of 74 (27 per cent) routine determinations preceding nembutal were compatible. On the other hand, 55 of 74 (74 per cent) of the SMR determinations agreed with the clinical diagnosis (Table 4).

Of the 19 determinations of the SMR which failed to fall in the normal range only 1 was below −13 per cent. This value of −22 per cent was recorded in a patient who had a nodular goiter and symptoms suggestive of

TABLE 3. DETERMINATION OF PBI, BMR AND SMR: SUMMARY OF RESULTS IN 42 HYPERTHYROID PATIENTS

	Number of determinations	Average results
PBI	36	8.7 mcg. %
Previous average BMR	23	+48%
BMR Immediately preceding IVN*	75	+46%
SMR	75	+33%

* Intravenous nembutal.

hypothyroidism, although the final clinical diagnosis was euthyroidism. The remaining 18 determinations were only slightly above +3 per cent, the average being +8 per cent. Except for 1 value of +13 per cent and 1 of +12 per cent, all were below +10 per cent.

Hyperthyroidism

Seventy-five determinations of the SMR were made on 42 patients in this group. Results are presented in Table 3.

The average of 36 determinations of the PBI was 8.7 micrograms per cent. The average of previous determinations of the BMR in 23 instances was +48 per cent, the average BMR immediately preceding nembutal in 75 instances was +46 per cent and the average SMR in 75 instances was +33 per cent. There was an average fall of 13 points between the BMR preceding nembutal and the SMR.

The blood protein-bound iodine was compatible with the clinical diagnosis in 30 of 36 determinations (83 per cent) (Table 4). In the remainder

the blood iodine was not determined or was not considered valid because of exogenous iodination. Of the 6 values for the PBI which did not agree with the clinical diagnosis, 4 were borderline values ranging from 5.6 to 6.2 micrograms per cent. A value of 4.8 micrograms per cent was recorded in a patient with characteristic symptoms of toxic nodular goiter undergoing preoperative preparation with iodine, and a value of 4.1 micrograms per cent in a patient with recurrent Graves' disease. In the 6 instances in which the PBI was not compatible with the clinical diagnosis, the SMR was compatible.

TABLE 4. PBI, BMR AND SMR: COMPATIBILITY WITH CLINICAL DIAGNOSIS IN 200 PATIENTS

	Clinical classification							
	Hypothyroid		Euthyroid		Hyperthyroid		All patients	
	No.	%	No.	%	No.	%	No.	%
PBI	30/41	73	39/47	83	30/36	83	99/124	80
Previous average BMR	11/29	38	12/42	29	75/75	100	98/146	67
BMR Immediately Preceding IVN*	29/51	57	20/74	27	75/75	100	124/200	62
SMR	51/51	100	55/74	73	75/75	100	181/200	91

* Intravenous nembutal.

Twenty-three of these patients had previous determinations of the BMR, of which all (100 per cent) were above the range of normal. Likewise 75 of 75 (100 per cent) routine determinations preceding nembutal were compatible with the diagnosis. All of the 75 determinations of the SMR remained above the normal range (Table 4).

General

In our entire series the PBI was compatible with the clinical diagnosis in 80 per cent of the cases, the previous average BMR in 67 per cent, the BMR preceding nembutal in 62 per cent, and the SMR in 91 per cent (Table 4). We believe the PBI to be significantly more reliable than is indicated by our statistics. For a period of several weeks in the middle of this study incompatible results with the PBI were especially frequent. Careful investi-

gation revealed this to be due to the variable reducing power of one of the reagents (phosphorous acid) used in our method. This was corrected and reliability of results was re-established. We could not conscientiously eliminate these values and have accordingly included them to the detriment of the PBI data. In a previous report from this clinic the PBI was in agreement with the clinical diagnosis in 91 per cent of the cases (22). Moreover, our extensive experience with the blood iodine covers a period of over twenty years, whereas we have been determining the SMR for only slightly over a year. Thus, we believe that the value of the blood iodine is firmly established. Although the SMR has been of significant help, we cannot but feel that more extensive statistics from this and other clinics should be forthcoming before the procedure is finally evaluated.

DISCUSSION

The clinical diagnosis of clear-cut hypothyroidism is seldom difficult. In borderline cases, however, the diagnosis is often obscured by contradictory symptoms. Indeed, we recognize an entity which we designate "agitated hypothyroidism," which responds to desiccated thyroid therapy, although many of the symptoms suggest thyrotoxicosis. In such instances, because of underlying nervousness or anxiety, the BMR is often normal or even elevated. Since extrathyroidal hypermetabolism does not affect the blood protein-bound iodine, this latter test has been helpful as a diagnostic aid in such cases. Determination of the somnolent metabolic rate, *i.e.*, the BMR determined under intravenous nembutal anesthesia, has been most helpful.

Not infrequently patients with normal thyroid function present themselves with symptoms suggestive of thyrotoxicosis, a diagnosis tentatively supported by elevation of the BMR. Patients with such extrathyroidal hypermetabolism are occasionally subjected to thyroidectomy and often the postoperative symptoms persist or become worse. The differential diagnosis in such instances may be extremely difficult. We have found the somnolent metabolic rate reliable in unmasking the true state of metabolism.

Patients with clear-cut evidence of hyperthyroidism may have an element of superimposed extrathyroidal hypermetabolism which adds to the height of an already elevated BMR. It is often difficult clinically to dissociate the thyrotoxicosis from the hypermetabolism and thus clearly evaluate the degree of hyperthyroidism. The SMR often aids in differentiating these two entities.

Extrathyroidal hypermetabolism, on the other hand, is not necessarily associated with hyperthyroidism. In such instances the SMR approximates the BMR in value.

The SMR appears to be of value in following hyperthyroid patients who are being prepared for surgery. We have found close correlation between this value and the clinical improvement noted in response to careful preparation.

Criticism might be directed toward determination of the SMR on the basis that standards for the metabolic rate have been determined with patients in a waking state, and results for metabolic rates determined under anesthesia would require new standards before they could be properly interpreted. From a statistical viewpoint this is undoubtedly true. However, from the viewpoint of the clinician, it is pertinent to point out that in none of our patients with clinical hyperthyroidism did the SMR fall within the range of normal. In only 1 patient with clinically normal thyroid function did the SMR fall below the range of normal, and in this patient there was suggestive clinical evidence of hypothyroidism. In addition, all patients with clinical hypothyroidism, normal BMR, and SMR below the normal range, improved on desiccated thyroid therapy.

Bartels reported that in normal patients the metabolic rate dropped an average of 13 per cent under pentothal anesthesia, whereas in patients with hyperthyroidism it showed only a slight decrease (20). In our series there was little difference in the fall under nembutal between hypothyroid, euthyroid and hyperthyroid patients, the average being 14, 15 and 13 points, respectively. However, if those patients with a clinical diagnosis of extrathyroidal hypermetabolism are separated from the others, the fall is reduced considerably. The SMR in 15 hypothyroid patients with underlying nervous states fell an average of 30 points, whereas the remainder fell an average of only 7 points. In the group of patients considered clinically to have normal thyroid function, the average fall in 18 with underlying nervous states was 34 points, but the remainder fell an average of only 10 points (Table 5). In hyperthyroid patients it is difficult to separate extrathyroidal hypermetabolism from true hyperthyroidism and we can conclude only that the fall varies, probably dependent upon the degree of extrathyroidal hypermetabolism.

We have come to rely to a large extent upon the PBI as a diagnostic aid in the differential diagnosis of thyroid disorders. Exogenous iodine, however, in any form, affects the PBI so definitely that we no longer determine the PBI in the face of known iodination. Because of misleading results of the BMR and the serum cholesterol in some instances we have been left with no satisfactory laboratory aid in such circumstances. Although radioactive iodine tracer studies appear fairly reliable, not only are they of questionable value in the face of iodination but as yet this specialized test is limited to centers where I^{131} is available. The SMR appears to be a

satisfactory substitute in patients who have had exogenous iodine, and is an acceptable supplementary procedure in noniodinated patients.

Moreover, the BMR and the PBI indicate different aspects of thyroid function. The former is an index of the total effect of thyroid hormone on end organs, and its level depends both on the amount of hormone and the sensitivity of the end organs. The PBI, on the other hand, represents the amount of circulating thyroid hormone and is dependent upon the functional activity of the thyroid gland (5). Radioactive iodine tracer studies also give information as to the functional activity of the thyroid gland as indicated by the uptake of I^{131}.

In 7 instances (3.5 per cent of 200 cases) the SMR was, on the average,

TABLE 5. AVERAGE FALL IN METABOLIC RATE FOLLOWING NEMBUTAL ANESTHESIA IN PATIENTS WITH UNDERLYING NERVOUS STATES, AS COMPARED WITH ALL OTHERS

	Average fall of metabolic rate under nembutal anesthesia	
	Patients with underlying nervous states	All other patients
Hypothyroidism	30%	7.0%
Euthyroidism	34%	10.0%
Both groups	32%	8.5%

5.7 per cent *higher* than the routine BMR immediately preceding it, and in 8 instances (4 per cent of 200 cases) the results of the SMR and the BMR were identical. We are unable to explain these cases in which the somnolent rate was higher than the routine basal rate.

Although determination of the BMR under sodium pentothal anesthesia as reported by Bartels (20) is a sound procedure when performed in a hospital with the assistance of a trained anesthetist, testing cannot be done safely under any less rigid conditions. Determination of the SMR as we have described it, however, can be safely performed as an office procedure. We have made over 250 determinations without serious complication. In 4 instances nausea and vomiting lasting twenty-four hours was observed.

Often the BMR must be determined serially before a test is obtained which is considered satisfactory. Apprehensive individuals, especially, must become familiar with the procedure before they are able to relax sufficiently to produce a reliable determination. The expense to such pa-

tients of multiple testing, as well as the time lost in instituting treatment, is considerable. Indeed, some patients never become sufficiently adjusted to insure a satisfactory BMR. Moreover, the basal metabolic rate may be erratic in serial determination, even in patients emotionally well adapted. Perhaps the SMR will be a solution in such instances, so that the initial determination will be a clinically significant indicator of thyroid function. Figure 2 illustrates the relative consistency of the BMR and the SMR in serial determinations.

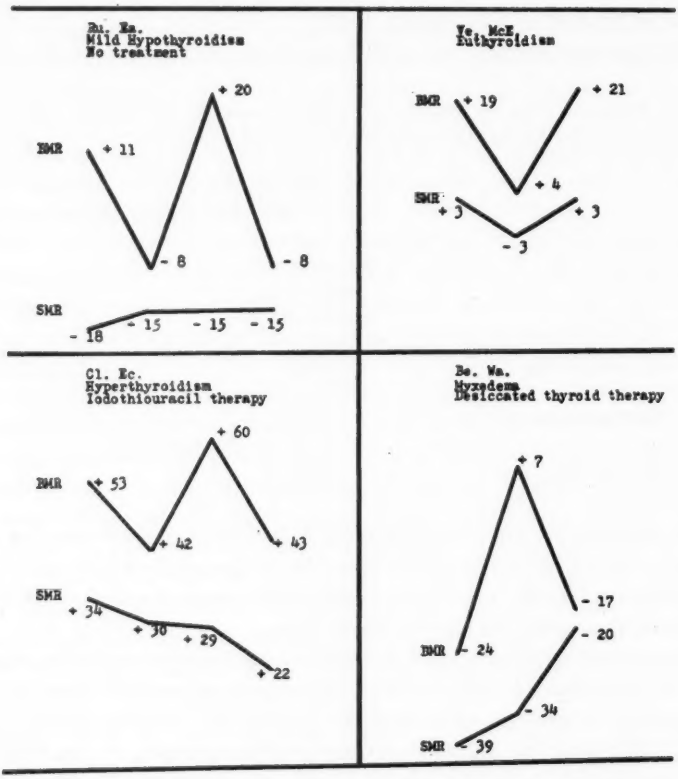

FIG. 2. BMR and SMR: relative consistency of serial determinations.

CONCLUSION

It is our conclusion that the final diagnosis of thyroid dysfunction must be established primarily on the basis of *clinical* evidence. The basal metabolic rate is frequently not compatible with the best clinical judgment and may be misleading. The somnolent metabolic rate, on the other

hand, appears a better index of the true metabolic state. When the latter is intelligently interpreted, along with the serum protein-bound iodine and radioactive iodine tracer studies, the confused picture of borderline thyroid dysfunction may become clarified.

SUMMARY

1. A method has been described for determination of the metabolic rate under intravenous nembutal anesthesia. We have designated this the *somnolent metabolic rate* (SMR).

2. Two hundred determinations of the SMR in 152 patients with varying degrees of normal, elevated and depressed thyroid function have shown excellent correlation with both the clinical diagnosis and the serum protein-bound iodine. Ninety-one per cent of the SMR determinations were compatible with the clinical diagnosis, whereas only 67 per cent of previous average BMR determinations and 62 per cent of BMR determinations immediately preceding nembutal, showed compatibility.

3. The average fall of the metabolic rate in hypothyroid and euthyroid patients with a clinical diagnosis of underlying nervous states was 32 per cent, whereas the average fall in other patients in these two groups was only 8.5 per cent. In hyperthyroid patients it was difficult clinically to separate extrathyroidal hypermetabolism from true hyperthyroidism. The average fall in all patients in this group was 13 per cent, as compared to 14 per cent in hypothyroid patients and 15 per cent in euthyroid patients.

4. The following advantages of the SMR have been indicated:

a. Intravenous nembutal requires neither hospitalization nor the assistance of a trained anesthetist, but may be used as an office procedure in determination of the SMR.

b. Single determinations of the BMR are unreliable and serial determinations may be erratic, whereas initial single determinations of the SMR give significant information as concerns thyroid function and its effect on the organism.

c. In hypothyroid patients with normal or elevated basal metabolic rates the SMR will frequently unmask the true diagnosis.

d. In euthyroid patients with elevated basal metabolic rates the SMR will frequently reveal the rate to be elevated as a result of extrathyroidal hypermetabolism rather than of true hyperthyroidism.

e. Hyperthyroid patients often have an element of extrathyroidal hypermetabolism to add to an already elevated BMR. The SMR, when compared to the BMR, aids in differentiating these two components.

f. Although the serum protein-bound iodine is generally accepted to be more reliable than the BMR as an indicator of functional thyroid dis-

orders, values for the PBI may be affected by exogenous iodine in any form and are of doubtful value in iodinated patients. Radioactive iodine tracer studies may also be affected by exogenous iodine. The SMR appears to be a satisfactory laboratory diagnostic aid in such instances.

g. The PBI represents the amount of circulating thyroid hormone and is dependent upon the functional activity of the thyroid gland. The uptake of I^{131} by the thyroid also depends upon functional activity of the gland. On the other hand the basal metabolic rate and, more effectively, the *somnolent* metabolic rate, is an index of the *total* effect of thyroid hormone on end organs. Consequently, its level depends upon the sensitivity of the end organs as well as the amount of available hormone. Since the PBI, the SMR and I^{131} tracer studies indicate different aspects of metabolism, all three should be determined in patients suspected of having thyroid dysfunction.

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CHRONIC THYROTOXIC MYOPATHY: REPORT OF A CASE*

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MASQUERADING behind the clinical picture of an apparently fatal case of progressive muscular atrophy, one occasionally discovers an unusual form of thyrotoxicosis called chronic thyrotoxic myopathy, and thus the apparent ultimately fatal prognosis of the disease is dramatically altered. Furthermore, undiscovered, this clinical entity is fairly rapidly fatal.

CASE REPORT

A. S., Case No. 586196, a 35-year-old white male welder, entered the Henry Ford Hospital on September 7, 1949, because of irritability, nervousness, marked weakness and tremor. He had been in good health until one year prior to admission, at which time he had a severe illness characterized by sharp pains in the back radiating around to the anterior chest. The pains were increased by breathing but not associated with cough or fever. The pains persisted for from four to six days and then subsided, never to recur.

Since that time he had noted the insidious development of easy fatigability and lack of ambition and responsibility, to the extent that he soon could work only two or three days each week. He was previously "happily" married, the father of four girls, but began to have periods in which he would become very irritable with his family, periods in which he would leave for work and not return home for three or four days, and other domestic difficulties which led his wife to contemplate divorce proceedings.

About nine months prior to admission a tremor of the hands and a progressive weakness of the upper extremities developed. Because of this, he had to discontinue his welding job about ten months after the onset of symptoms. He attempted to become a waiter, but had to give up because he dropped the trays. This tendency to drop things he attributed to tremulousness and incoordination of the arms. About this time he also noted the appearance and progression of coarse muscle twitchings of the upper arm which gradually spread to the shoulders, back of the neck, spinal muscles and thighs. During the preceding six months there had been a 30-pound weight loss, despite a ravenous appetite, increasing nervousness and irritability, an intolerance to heat, and a gradual loss of libido. The remainder of the patient's past history and family history was noncontributory, except that one aunt had had thyrotoxicosis.

Physical examination on admission showed a well nourished white male lying quietly in bed. His temperature was 99.2° F., pulse 120, respirations 24, and blood pressure 135/80 mm. of Hg. His weight was 152 pounds (69.1 Kg.) and his height, 5 feet 7 inches (170 cm.). The skin was warm and moist.

He showed a marked bilateral symmetrical muscular atrophy of the shoulder girdle

Received for publication June 7, 1951.

* Read by title at the Annual Meeting of the Association for the Study of Internal Secretions, Atlantic City, N. J., June 7–9, 1951.

FIG. 1. The patient in September, 1949, before treatment. Note the atrophy of the deltoid, infraspinatus, supraspinatus, and trapezius muscles.

FIG. 2. January 21, 1950, four and one-half months after beginning treatment with propylthiouracil. Note marked improvement in muscles of the shoulder girdle.

with marked wasting of the supraspinatus, infraspinatus, trapezius and deltoid muscles (Fig. 1). Periodic coarse fasciculations of the muscles of the shoulder, upper arm, back and posterior thighs were noted. He did not have exophthalmos or other eye signs. There was a fine tremor of the tongue and a coarse tremor of the hands. The thyroid gland was not considered enlarged and no nodules or bruit were noted. The lungs, heart, and abdomen were normal, except for a regular tachycardia. The genitalia were normal and no testicular atrophy was noted.

Neurologic examination showed only the atrophy and coarse fasciculations. Cranial nerves were normal. Deep tendon reflexes in the upper and lower limbs were brisk but definitely not hyperactive; plantar responses were flexor. There was no sensory defect.

Laboratory examinations revealed the following: The Kline exclusion test for syphilis gave negative results. The specific gravity of the urine was 1.021 with no protein or sugar. The urinary sediment contained a few leucocytes. Blood hemoglobin was 14.2 grams per cent. The white blood cell count was 8,700, and the blood smear appeared normal. Blood nonprotein nitrogen was 31 mg. per cent; fasting blood sugar, 76 mg. per cent; cholesterol, 163 mg. per cent; sodium, 303 and 315 mg. per cent; potassium, 17.8 and 18.9 mg. per cent; calcium, 11.6 mg. per cent; phosphorus 4.7 mg. per cent; and alkaline phosphatase, 3.3 Bodansky units. The 24-hour urine contained no lead or porphobilinogen, and the calcium content was 282 mg. Urinary 17-ketosteroids were 10.6 mg. per twenty-four hours (normal levels for a male of this age in this laboratory are 17 to

20 mg. (1)). The oral three-hour glucose tolerance test showed a slightly impaired tolerance. Total plasma iodine was 10.4 micrograms per cent. Arm-to-tongue circulation time (decholin) was ten seconds, and the arm-to-lung circulation time (ether), six seconds. Tests showed muscle strength to be unchanged after administration of prostigmine or quinine. While on a low creatine-creatinine diet he excreted, on two occasions, 0.143 gram and 0.267 gram of creatine in twenty-four hours. The adrenalin test for adrenal cortical function showed a normal fall in eosinophil count (2). The chest was normal on x-ray examination; there was no evidence of substernal thyroid. Biopsy of the left trapezius muscle revealed a marked fibrous replacement of muscle tissue, loss of striae, fragmentation of the muscle fibers, and degeneration of the muscle nuclei. The basal metabolic rate before treatment ranged from +36 to +47 per cent.

While in the hospital the patient had a persistent tachycardia, even with bed rest. His basal metabolic rate remained elevated, and his weight decreased steadily from 152 pounds (69.1 Kg.) to 141 pounds (62.9 Kg.) in eight days.

Therapy. Propylthiouracil therapy was started in a dose of 300 mg. daily, on the eighth hospital day, which was the day of discharge. On readmission six weeks later, the interim improvement was striking. He reported marked subsidence of his nervousness and irritability and improvement of his strength about nine days after therapy was started. Shortly thereafter the muscle fasciculations ceased. He returned to his former occupation of welding and was advanced to foreman in two weeks.

His weight at the time of the *second hospital admission* was 162 pounds, a gain of 21 pounds in six weeks. The pulse was 90, and the blood pressure 120/70 mm. of Hg. No muscle fasciculations were noted and only moderate atrophy of the shoulder-girdle muscles was evident. The basal metabolic rate was +6 per cent. Urinary 17-ketosteroids were now 14.6 mg. per twenty-four hours. Objective tests of muscle strength (hand grip and step-up tests) gave normal results. The patient was again discharged, to continue on propylthiouracil, 150 mg. per day. The blood count had remained essentially normal.

At the time of his *third hospital admission*, approximately four and a half months after the beginning of propylthiouracil treatment, the patient was essentially asymptomatic, except for continued lack of libido and slight nervousness in the two weeks prior to his readmission. His former irritability recurred and he had one period of four days' duration when he did not go to work or return home. His daughter remarked, "Daddy, you're cross with us again. Did you forget to take your pills?" His wife again was led to wonder if his difficulties were her fault and asked her physician if she should proceed with a divorce.

His weight was 156 pounds, blood pressure was 130/99 mm. of Hg, and pulse 104 to 120 per minute. There was a fine tremor of the hands. The isthmus and lobes of the thyroid were barely palpable.

No muscle fasciculations were noted. There was no objective evidence of muscular weakness, and only minimal atrophy of the shoulder girdle (Fig. 2). The BMR had risen to +34 per cent. Urinary 17-ketosteroids were 6.6 mg. per twenty-four hours. There was spontaneous creatinuria—0.093 Gm. per twenty-four hours. Propylthiouracil was increased to 300 mg. per day and methyltestosterone linguets were started in a dose of 20 mg. per day.

His *fourth hospital admission* was on September 16, 1950, one year after starting propylthiouracil. At this time he was entirely asymptomatic. There was no evidence of muscle atrophy or any other abnormality on physical examination. He had been taking 200 mg. daily of propylthiouracil for the previous six months and methyltestosterone linguets, 20 mg. daily. His BMR was now +4 per cent. His blood count was normal.

He was working regularly and his wife reported normal domestic relations and an absence of the previously noted personality aberrations.

DISCUSSION

Chronic thyrotoxic myopathy is characterized by: 1) progressive, symmetrical, muscular weakness and atrophy which most frequently involves the shoulder and pelvic girdle; 2) usually minimal symptoms and signs of thyrotoxicosis; and 3) dramatic improvement or cure by adequate treatment of the hyperthyroidism. With this clinical picture, it can be readily understood why this disease has been confused with progressive muscular atrophy, with its hopeless prognosis.

Chronic thyrotoxic myopathy was first described by Bathhurst (3) in 1895; McEachern and Ross (4) summarized the literature till 1942, reporting 13 cases, of which 3 were their own. These authors excluded 3 previously reported cases because of insufficient data. Thorn and Eder (5) reported 5 cases and Bartels and Pizer (6), one more. Nineteen confirmed cases have been recorded to date.[1] In 4 of the previously reported 19 cases, a diagnosis of progressive muscular atrophy had been made and death from respiratory paralysis occurred. The correct diagnosis of chronic thyrotoxic myopathy was not made until postmortem examination or until the patient was moribund.

The manifestations of impaired muscle function in thyrotoxicosis fall into two major groups (7); the first group comprises the thyrotoxic myopathies in which muscular disturbances are a direct consequence of the hyperthyroidism; in the second group, thyrotoxicosis coexists with an independent myopathy, of which the manifestations are exaggerated or made overt by the thyrotoxic state.

Group I:

(a) Cases of thyrotoxicosis with generalized muscular weakness unassociated with significant muscular wasting or atrophy.

(b) Cases of chronic thyrotoxic myopathy.

(c) Cases of thyrotoxicosis with ophthalmoplegias with or without exophthalmos.

Group II:

(a) Thyrotoxicosis coexisting with myasthenia gravis.

(b) Thyrotoxicosis coexisting with familial periodic paralysis.

As to the clinical picture of chronic thyrotoxic myopathy, an analysis

[1] Since submitting this article for publication, 10 additional cases have been recorded by K. L. Zierler (Muscular wasting of obscure origin and the thyroid gland, *Bull. Johns Hopkins Hosp.* **89**: 263–280 (Oct.) 1951).

of the 19 cases previously reported (3–6) shows a striking difference in the sex ratio, the males predominating in a ratio of 3:1. This is in contradistinction to the usual sex ratio of uncomplicated thyrotoxicosis. The patients ranged in age from 22 to 62 years, with by far the majority in the fifth decade or past.

The onset of the disease was gradual, usually leading to hospitalization within a year. Characteristically, all patients experienced marked weakness and weight loss ranging from 17 to 68 pounds, with an average loss of 35 pounds. Tachycardia and elevated systolic blood pressure with increased pulse pressure were also characteristic. There was no exophthalmos in 11 of the 19 cases. In one third of the cases there was no visible or palpable enlargement of the thyroid gland.

A tremor of the hands and generalized coarse rapid fasciculations of the muscles were present in the majority of patients. The muscle atrophy was most marked in the shoulder girdle in 13 of the 19 cases.

The basal metabolic rates ranged from +29 per cent to +100 per cent, with the majority over +40 per cent.

Spontaneous creatinuria was present in the 9 patients in whom determinations were made, and there was impaired retention of creatine (28 per cent and 68 per cent) in the 2 subjects in whom the creatine tolerance test was performed.

Urinary 17-ketosteroids were determined in 4 patients (5) and were found to be low in 3. In 2 of the latter, both males, there was some residual weakness persisting after treatment of the thyrotoxicosis. Since gonadal atrophy had been noted in both, they were given testosterone with complete recovery.

Muscle biopsy in at least 2 of the patients was reported as showing the typical findings described by Askanazy (8), namely degenerative atrophy of the muscle cells, fatty infiltration, loss of striae, degeneration and vacuolization of muscle nuclei, and fibrous replacement of muscle cells.

Four of the 19 patients died, the terminal picture in each being respiratory paralysis. Of the remaining 15 subjects, all were treated surgically except 3, 1 of whom was treated with thiobarbital and 2 with thiouracil; all cases showed dramatic recovery following treatment.

Patients with chronic thyrotoxic myopathy exhibit several findings in common with patients having one of the progressive muscular dystrophies (7). Both exhibit increased creatine excretion, a low creatinine coefficient, a lessened capacity to retain ingested creatine, and extra creatine excretion following administration of glycine. However, the administration of iodine, or thiouracil, or thyroidectomy will correct this abnormality in creatine metabolism in chronic thyrotoxic myopathy. It is without effect in progressive muscular dystrophy. Cases of the latter include the facioscapulo-

humeral type of Landouzy and Dejerine, the pseudohypertrophic form, and Erb's juvenile type.

These dystrophies tend to occur in a younger age group than does chronic thyrotoxic myopathy. They usually have their onset in childhood (although some have been reported as having their onset past the age of 60) and they are generally familial. The defect is inherited as a Mendelian dominant sex-linked characteristic. Muscle twitchings or fibrillations are not seen in these cases and pseudohypertrophy often precedes the atrophy. Muscle biopsy in a typical case shows a remarkable proliferation of the sarcolemma nuclei.

Cases of progressive muscular atrophy, which include Aran-Duchenne's type, the Werdnig-Hoffman type, and amyotrophic lateral sclerosis, also present the abnormal creatine-creatinine metabolism above, as well as localized muscle wasting. They differ, however, in that they tend to affect the distal muscle groups first, whereas in chronic thyrotoxic myopathy it is the proximal muscle groups (shoulder and pelvic girdle) which are the earliest and most severely affected. In progressive muscular atrophy one usually finds fine muscle fibrillations rather than the coarse, rapid, flash-like fasciculations. The weakness and fatigability are in proportion to the muscle wasting, rather than considerably out of proportion as in cases of chronic thyrotoxic myopathy. There is evidence of involvement of the corticobulbar and corticospinal tracts (lesions of which give spasticity and pathologic reflexes). These patients do not have the tachycardia, profuse perspiration, hand tremors, irritability, emotional instability and heat intolerance characteristically seen in chronic thyrotoxic myopathy. The basal metabolic rate is within normal limits.

In view of the brisk muscular twitchings seen in cases of the muscular atrophies such as amyotrophic lateral sclerosis, an elevation of the basal metabolic rate might be expected; but McEachern and Ross studied 9 such cases and found this not to be true (4).

Of value in diagnosis, also, is the elevation of protein-bound iodine in cases of chronic thyrotoxic myopathy. In unusual instances, chronic thyrotoxic myopathy might be confused with heavy-metal poisoning, cervical disc syndrome, and other primary myopathies.

As a laboratory tool for the diagnosis of thyrotoxicosis the presence of spontaneous creatinuria and a positive creatine tolerance test are receiving more and more emphasis. The current concept of creatine metabolism, briefly stated, is as follows (5): The amidin group of arginine is conjugated with glycine in the kidney to form glycocyamine, the unmethylated precursor of creatine. The glycocyamine formed is methylated in the liver by transfer of a methyl radical from the pool of labile methyl groups (chiefly from choline and methionine) to form creatine. Ninety-eight per cent of

the creatine thus formed is then stored in the muscles, 20 per cent to 40 per cent in the form "free" creatine and the remainder phosphorylated to phosphocreatine. This latter substance is a high-energy phosphate ester which furnishes the phosphate group for the reformation of adenosine triphosphate from adenyl phosphate. The breakdown of adenosine triphosphate to adenyl phosphate has the closest known energy linkage with actual muscle contraction. With the breakdown of the phosphocreatine, creatinine is formed as a waste product and excreted in the urine.

Creatine is excreted in the urine (9) in the normal adult male in insignificant quantities. Children and adult females may excrete moderate amounts. In certain of the myopathies, including thyrotoxicosis, there is an abnormal spontaneous creatinuria and administration of an oral dose of creatine results in an abnormally high excretion of this substance. The normal adult male retains about 80 per cent and the female 70 per cent of the test dose of creatine, whereas patients with thyrotoxicosis will retain only 25 per cent to 75 per cent and patients with myxedema may retain 100 per cent. As stated previously, iodine, antithyroid drugs, and thyroidectomy correct this creatine defect in patients with thyrotoxicosis.

As to the value of spontaneous creatinuria and the creatine tolerance test in the diagnosis of hyperthyroidism, Sohval *et al.* (10) have found that 18 per cent of "normals" will have either a spontaneous creatinuria or positive results from a creatine tolerance test, whereas 90 per cent of patients with thyrotoxicosis will have either of these findings and 50 per cent will have both. No quantitative difference in creatine excretion has been noted between patients with chronic thyrotoxic myopathy and patients with uncomplicated thyrotoxicosis.

The fundamental metabolic defect (or defects) in chronic thyrotoxic myopathy has not been found. Thorn has postulated that the combination of thyrotoxicosis and steroid hormone deficiency can cause myopathy (5). Two of his male patients had testicular atrophy and low 17-ketosteroid excretion and a third, a female, showed adrenal gland necrosis at autopsy. Our patient exhibited a low 17-ketosteroid excretion and a loss of libido; there was improvement in libido coincident with complete recession of muscle atrophy, only after treatment was supplemented with methyltestosterone.

SUMMARY

This report concerns a case of chronic thyrotoxic myopathy with marked progressive symmetrical muscular weakness and atrophy of the shoulder girdle. Abnormality of creatine-creatinine metabolism was a prominent feature. Personality aberration, nervous irritability, and loss of libido, although presented as complaints of secondary importance, had threatened this patient's domestic status.

Treatment with propylthiouracil resulted in dramatic reversal of the thyrotoxicosis with marked improvement of the myopathy and personality deviations. Supplemental treatment with methyltestosterone was associated with complete remission of the myopathy and restoration of personality equilibrium.

The syndrome of thyrotoxic myopathy is rare but clinically important because it can be confused with the usually fatal primary myopathies, especially progressive muscular atrophy.

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LETTERS to the EDITOR

THYROID UPTAKE MEASURED ONE HOUR AFTER SMALL ORAL DOSES OF RADIOIODINE*†

To the Editor:

Since the early demonstration (1) of the feasibility of radioiodine uptake as a clinical measure of thyroid function, many modifications in procedure and dosage have been introduced (2, 3). Werner *et al.* (4) recently summarized an extensive study measuring the per cent of I^{131} accumulated in the thyroid gland twenty-four hours after carrier-free oral doses. These authors concluded this procedure was the most acceptable for appraising thyroid function in routine clinical practice.

Because a significant overlap exists between the euthyroid and hyperthyroid groups when 24-hour uptakes are measured, Kriss (5) introduced the technic of measurement of per cent of administered dose in the thyroid one hour after intravenous injection. This author concluded that such a procedure resulted not only in an increase in rapidity of the diagnostic test but also more satisfactory differentiation between the euthyroid and hyperthyroid state in a group of untreated patients.

It is the purpose of this communication to present data suggesting that the oral method of I^{131} administration in a one-hour test gives comparable results to that of Kriss (5) in measuring the iodine accumulating function of the thyroid. The oral route offers the further advantages of ease and simplicity of preparation and handling of doses with a minimum of radiation exposure. The use of special gamma-sensitive G-M counters or scintillation counters makes doses even as low as 0.2 microcurie sufficient for measurement at one hour.

Radioiodine in carrier-free solution was orally administered to fasting patients with no gastro-intestinal dysfunction. Ten of these patients who were hyperthyroid and 2 who were euthyroid also received radioiodine intravenously for comparison of results. Forty-nine observations were made

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* Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

† The radioiodine used in this investigation was supplied by Oak Ridge National Laboratory on authorization from the Isotopes Division, U. S. Atomic Energy Commission.

in 33 patients. Twelve were euthyroid and 21 were hyperthyroid as demonstrated by subsequent clinical course and response to specific therapy. The test results were obtained prior to any antithyroidal therapy.

A comparison of the one-hour uptake with that at twenty-four hours (Fig. 1) demonstrates at least a similar accuracy, whether the I^{131} is ad-

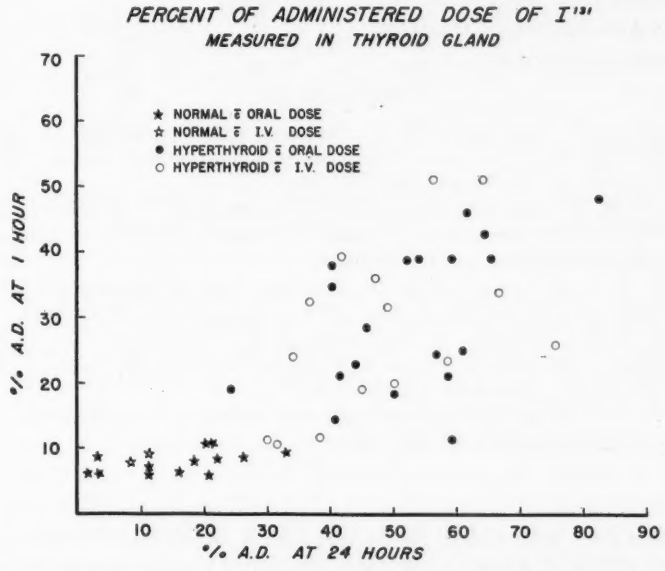

FIG. 1. The ordinate represents the per cent of the administered dose of radioiodine at one hour as observed by *in situ* measurement over the thyroid gland. The 24-hour values are represented by the abscissa. The 34 observations above 11 per cent at one hour were made on 21 hyperthyroid patients; the 12 euthyroid patients gave results below 11 per cent, in the 15 observations made. The patients in this series had received no previous antithyroidal therapy and their thyroid function was verified by the subsequent clinical course.

ministered orally to the fasting patient or intravenously. A one-hour value of 11 per cent appears to be the maximum uptake for our euthyroid group. When measured at twenty-four hours 2 cases of hyperthyroidism in this series showed uptake values in the euthyroid range, and 6 more showed values in the equivocal range (30 to 40 per cent). Five of the hyperthyroid patients had one-hour uptake values of less than 15 per cent.

A measurement at the end of one hour thus gives results of at least similar accuracy to that at twenty-four hours, with a great saving in time. Because of ease of administration and minimal radiation exposure the oral route of administration is preferred to the intravenous. In the absence

of impaired gastro-intestinal function, the oral route test is as accurate as the intravenous.

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ACNE AND GYNECOMASTIA FOLLOWING I^{131} THERAPY FOR HYPERTHYROIDISM*

To the Editor:

The only complications described to date following the administration of therapeutic doses of I^{131} for hyperthyroidism are temporary swelling and tenderness of the thyroid and myxedema, both generalized and circumscribed.

Of a series of 21 male patients with hyperthyroidism we recently had occasion to observe 6 in whom acne and gynecomastia developed following treatment with I^{131}. All 6 patients had moderately severe hyperthyroidism with diffuse enlargement of their thyroid glands and were treated with dosages of carrier-free I^{131} ranging from 2.64 millicuries to 12.6 millicuries. Their ages ranged from 26 to 41 years (Table 1).

Three of the patients complained, from fourteen to twenty-three days

* Reviewed by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions of the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

TABLE 1

Patient	Age	Sex	Dose of I^{131}	Acne	Gyneco-mastia
			(millicuries)		
J.K.	41	M	2.64	+	+
R.N.	36	M	12.60	+	0
L.P.	33	M	4.25	+	0
N.W.	26	M	5.29	+	0
E.W.	39	M	3.55	+	+
J.S.	30	M	5.32	0	+

after the administration of the therapeutic dose of I^{131}, of tenderness and swelling of both breasts. Examination of the breasts revealed definite enlargement and tenderness. The consistency was firm; there was no discoloration, no change in pigmentation of the nipples, nor was there secretion. Five patients noticed a skin eruption which they voluntarily brought to our attention. The eruption was typical of acne vulgaris with distribution mainly over the face, neck and trunk, the extremities being entirely spared.

Both acne and gynecomastia disappeared spontaneously two to four weeks after they were first noted. There were no other signs or symptoms and sexual function in the patients did not change during that period.

Two of the patients (R. N. and E. W.) were given additional therapeutic doses of I^{131} six months after the first dose, but none of the changes under discussion was noted at that time.

The cause of the changes reported is not entirely clear. It is reasonable to assume, however, that depression of thyroid function by I^{131} had stimulated the anterior pituitary to put out tropic hormones, not only to the thyroid (thyrotropic) but also to the adrenal cortex (corticotropic).

It has been shown that profound changes occur in the anterior pituitary following depression of the thyroid. The basophilic elements in the anterior lobe increase in the presence of even slight thyroxine deficiency. Severe thyroxine deficiency results in decrease in the acidophilic elements (1).

Goldberg and Chaikoff (2) studied rats which had been given I^{131} and found that their pituitaries were indistinguishable from those found after total thyroidectomy. Gorbman (3) described greatly enlarged pituitaries and increase of their chromophobe cells following administration of large amounts of I^{131} to rats.

The acne cannot be attributed to iodine. Only carrier-free I^{131} was used and the amounts of inorganic iodine in the doses administered were fractions of 1 microgram. The changes produced by I^{131} are most likely en-

tirely secondary to changes in thyroid function and not to concentration of I^{131} in the pituitary (2, 4). The most satisfactory interpretation seems to be that the changes in the thyroid brought about by I^{131} therapy lead to increased stimulation of the adrenal cortex by the pituitary. In cases of adrenal cortical hyperfunction, both primary and secondary to pituitary hyperactivity, acne and gynecomastia are known to occur.

Why the changes here described have not been observed after thyroidectomy remains unexplained.

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The Association for the Study of Internal Secretions

THE 1952 ANNUAL MEETING

The Thirty-fourth Annual Meeting of The Association for the Study of Internal Secretions will be held at the Palmer House, Chicago, Illinois, Thursday, Friday, and Saturday, June 5–6–7, 1952.

The Local Chairman of Arrangements is Dr. Willard O. Thompson.

All Scientific Sessions will be held in the Palmer House. The rooms in which each session will be held will be announced in the program and on the hotel bulletin board. The Annual Dinner is scheduled for Friday, June 7, at 7:30 P.M., preceded by cocktails at 6:30 P.M.

All members are urged to make hotel reservations immediately, inasmuch as the hotels expect to be filled to capacity. Make reservations directly with the Palmer House, advising time of arrival and departure date. Make your reservations now and avoid disappointment.

Those wishing to present papers, which will be limited to ten minutes, should send four copies of the title and abstract to the Vice-President, Dr. Evelyn Anderson, National Institutes of Health, Bethesda 14, Maryland, not later than *March 1, 1952. It is imperative that the abstracts be informative and complete with results and conclusions in order that they may be of reference value and suitable for printing in the program and journals of the Association.* The following regulations for the preparation of abstracts and titles must be carefully followed to insure consideration of the paper for the program:

1. Abstracts may not exceed two hundred words, or equivalent space, exclusive of title. No footnotes or acknowledgments to sponsors can be published. References, if used, must be placed in the body of the text. The abstract should consist of a single paragraph, if possible. Structural chemical formulas cannot be used.
2. The title heading must be arranged as follows:
   Line 1. Title, not to exceed fifteen words.
   Line 2. Author/s. The name of each nonmember-author collaborating with member-authors is to be followed by the phrase

"(by invitation)." Names of nonmembers who are introduced, *i.e.*, who are not collaborators with member-authors, are to be followed by the phrase "(introduced by . . .)." The principal degree, *e.g.*, M.D., of each author should be given after his name.

Line 3. Institution of origin and city in which institution is located.

3. The body of the abstract, typed double-space, should follow the heading. The original copy should be on bond paper. There should be three copies.
4. Abstracts should be letter-perfect, since there will be no opportunity for proofreading by authors.

1952 AWARDS AND FELLOWSHIPS

Fellowships

THE SCHERING FELLOWSHIP IN ENDOCRINOLOGY

This Fellowship will not be awarded in 1952, so that it may accumulate toward a $5,000 Fellowship to be awarded in 1953.

THE AYERST, McKENNA AND HARRISON FELLOWSHIP

The Ayerst, McKenna and Harrison Fellowship was first awarded in 1947 to Dr. Samuel Dvoskin and in 1948 to Dr. Ernest M. Brown, Jr. Dr. Brown was re-elected for the Fellowship in 1949. The 1950 Award was made to Dr. Lawrence E. Shulman.

Association Fellowships are designed to assist men or women of exceptional promise in their progress toward a scientific career in endocrinology. Fellowships may be awarded to an individual who possesses the Ph.D. or M.D. degree or to a candidate for either of these degrees. The stipend, which will not exceed $5,000, may be divided into two Fellowships in varying amounts in accordance with the qualifications of the appointee. The Committee will, in reviewing the proposed program of study, consider the amount of time which the Fellow intends to spend in course work and/or teaching. He must present evidence of scientific ability as attested by studies completed or in progress and/or the recommendation of responsible individuals. He must submit a program of proposed study, indicate one or more institutions where the proposed program will be followed, and submit statements of approval from the investigators with whom he proposes to conduct his research. He must serve full time if awarded a Fellowship. A small amount of time (10 to 15 per cent) may be allotted for course work or for participation in teaching, the latter purely on a voluntary basis.

Awards

THE E. R. SQUIBB AND SONS AWARD

The E. R. Squibb & Sons Award of $1,000 was established in 1939, and was given first in 1940 to Dr. George W. Corner; in 1941 to Dr. Philip E. Smith; in 1942 to Dr. Fred C. Koch; in 1944 to Dr. E. A. Doisy; in 1945 to Dr. E. C. Kendall; in 1946 to Dr. Carl G. Hartman; in 1947 to Drs. Carl F. and Gerty T. Cori; in 1948 to Dr. Fuller Albright; in 1949 to Dr. Herbert M. Evans; in 1950 to Dr. C. N. H. Long; and in 1951 to Dr. J. B. Collip. In 1943 no award was given. A special committee of five members of the Association selects the recipient from among investigators in the United States or Canada, on the basis of outstanding contributions to endocrinology.

Announcement of Increase in the E. R. Squibb and Sons Award

This Award has been increased to the amount of *$2,500* beginning with the 1952 Award.

(The Association expresses its sincere gratitude to E. R. Squibb and Sons for its interest in furthering research in this important field of medicine.)

THE CIBA AWARD

The Ciba Award, to recognize the meritorious accomplishment of an investigator not more than thirty-five years of age in the field of clinical or pre-clinical endocrinology, was established in 1942, but no recipient was selected in 1942 or 1943. In 1944 the award was presented to Dr. E. B. Astwood; in 1945 to Dr. Jane A. Russell; in 1946 to Dr. Martin M. Hoffman; in 1947 to Dr. Choh Hao Li; in 1948 to Dr. Carl Heller; in 1949 to Dr. George Sayers; in 1950 to Dr. Oscar M. Hechter; and in 1951 to Dr. Albert Segaloff. The Award is for $1,200. If, within twenty-four months of the date of the Award, the recipient should choose to use it toward further study in a laboratory other than that in which he is at present working, it will be increased to $1,800.

Nominations

Each member has the privilege of making one nomination for each Fellowship or Award. A nomination should be accompanied by a statement of the importance of the nominee's contributions to, or interest in, endocrinology and by a bibliography of the nominee's most important publications, with reprints if possible. The nominations should be made on special application forms which may be obtained from the Secretary, Dr. Henry H. Turner, 1200 North Walker Street, Oklahoma City 3, Oklahoma, and returned to him *not later than March 1, 1952.*

The American Goiter Association

THE 1952 ANNUAL MEETING

The next Annual Meeting of the American Goiter Association will be held in St. Louis, Missouri, May 1, 2 and 3, 1952, at the Hotel Chase. All those who plan to attend are urged to make hotel reservations immediately.

VAN METER PRIZE AWARD FOR 1952

The American Goiter Association again offers the Van Meter Prize Award of three hundred dollars and two Honorable Mentions for the best essays submitted concerning original work on problems related to the thyroid gland. Providing essays of sufficient merit are presented in competition, the Award will be made at the annual meeting of the Association which will be held in Saint Louis, Missouri, May 1, 2 and 3, 1952.

The competing essays may cover either clinical or research investigations; should not exceed three thousand words in length; must be presented in English; and a typewritten double-spaced copy in duplicate sent to the Corresponding Secretary, Dr. George C. Shivers, 100 East Saint Vrain Street, Colorado Springs, Colorado, *not later than March 1, 1952*. The committee, who will review the manuscripts, is composed of men well qualified to judge the merits of the competing essays.

A place will be reserved on the program of the annual meeting for presentation of the Prize Award Essay by the author, if it is possible for him to attend. The essay will be published in the annual Transactions of the Association.

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THE JOURNAL OF CLINICAL ENDOCRINOLOGY

Official Journal of the Association for the Study of Internal Secretions

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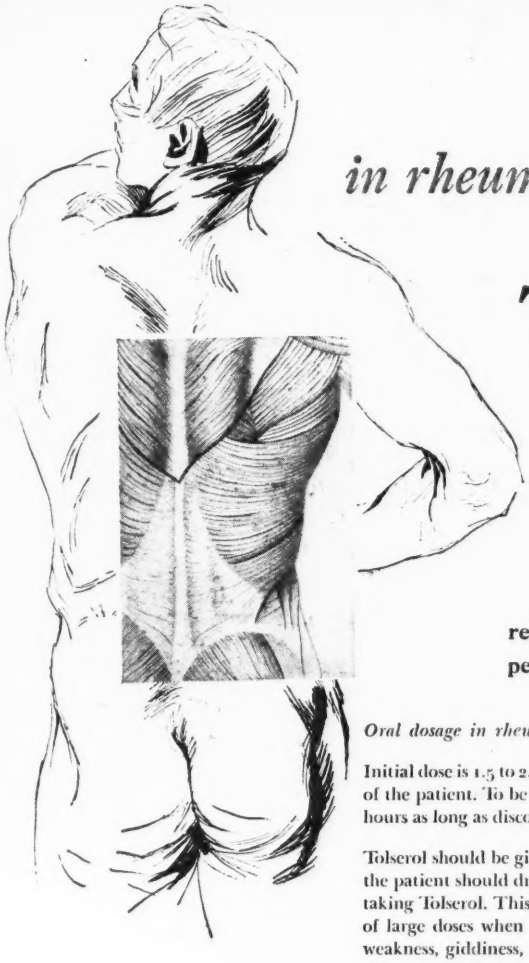

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